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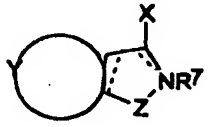

(I)

(57) Abstract

Compound, compositions containing compounds, methods of using compounds, and processes of making compounds, of formula (I) containing at least one ring nitrogen, or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer or mixtures thereof, wherein: X is double–bonded oxygen, or –OH; when R^7 is present, it is hydrogen or lower alkyl; y represents the atoms necessary to form a fused mono–, bi– or tricyclic, carbocylic or heterocylic ring, wherein each individual ring has 5–6 ring member atoms; and Z is (i) $–CH^2CHR^3–$ wherein R^2 and R^3 are independently hydrogen, alkyl, aryl or aralkyl; (ii) $–R^6C–CR^3–$ wherein R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, $–NO_2$, $–COOR^7$, or $–NR^7R^8$ where R^8 is independently hydrogen or $C_1–C_9$ alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5–6 ring members; (iii) $–R^2C=N–$; (iv) $–CR^2(OH)–NR^7$; or (v) $–C(O)–NR^7–$.

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OXO-SUBSTITUTED COMPOUNDS, PROCESS OF MAKING, AND COMPOSITIONS AND METHODS FOR INHIBITING PARP ACTIVITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to inhibitors of the nucleic enzyme poly(adenosine 5'-diphospho-ribose) polymerase ["poly(ADP-ribose) polymerase" or "PARP", which is also sometimes called "PARS" for poly(ADP-ribose) synthetase]. More particularly, the invention relates to the use of PARP inhibitors to prevent and/or treat tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury; neurological disorders and neurodegenerative diseases; to prevent or treat vascular stroke; to treat or prevent cardiovascular disorders; to treat other conditions and/or disorders such as age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (such as colitis and Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic and acute pain (such as neuropathic pain), renal failure, retinal ischemia, septic shock (such as endotoxic shock), and skin aging; to extend the lifespan and proliferative capacity of cells; to alter gene expression of senescent cells; or to radiosensitize hypoxic tumor cells.

2. Description of the Prior Art

Poly(ADP-ribose) polymerase ("PARP") is an enzyme located in the nuclei of cells of various organs, including muscle, heart and brain cells. PARP plays a physiological role in the repair of strand breaks in DNA. Once activated by damaged DNA fragments, PARP catalyzes the attachment of up to 100 ADP-ribose units to a variety of nuclear proteins, including histones and PARP itself. While the exact range of functions of PARP has not been fully established, this enzyme is thought to play a role in enhancing DNA repair.

During major cellular stresses, however, the extensive

activation of PARP can rapidly lead to cell damage or death through depletion of energy stores. Four molecules of ATP are consumed for every molecule of NAD (the source of ADP-ribose) regenerated. Thus, NAD, the substrate of PARP, is depleted by massive PARP activation and, in the efforts to re-synthesize NAD, ATP may also be depleted.

It has been reported that PARP activation plays a key role in both NMDA- and NO-induced neurotoxicity, as shown by the use of PARP inhibitors to prevent such toxicity in cortical cultures in proportion to their potencies as inhibitors of this enzyme (Zhang et al., "Nitric Oxide Activation of Poly(ADP-Ribose) Synthetase in Neurotoxicity", *Science, 263*:687-89 (1994)); and in hippocampal slices (Wallis et al., "Neuroprotection Against Nitric Oxide Injury with Inhibitors of ADP-Ribosylation", *NeuroReport, 5*:3, 245-48 (1993)). The potential role of PARP inhibitors in treating neurodegenerative diseases and head trauma has thus been known. Research, however, continues to pinpoint the exact mechanisms of their salutary effect in cerebral ischemia, (Endres et al., "Ischemic Brain Injury is Mediated by the Activation of Poly(ADP-Ribose)Polymerase", *J. Cereb. Blood Flow Metabol., 17*:1143-51 (1997)) and in traumatic brain injury (Wallis et al., "Traumatic Neuroprotection with Inhibitors of Nitric Oxide and ADP-Ribosylation, *Brain Res., 710*:169-77 (1996)).

It has been demonstrated that single injections of PARP inhibitors have reduced the infarct size caused by ischemia and reperfusion of the heart or skeletal muscle in rabbits. In these studies, a single injection of the PARP inhibitor, 3-amino-benzamide (10 mg/kg), either one minute before occlusion or one minute before reperfusion, caused similar reductions in infarct size in the heart (32-42%). Another PARP inhibitor, 1,5-dihydroxyisoquinoline (1 mg/kg), reduced infarct size by a comparable degree (38-48%). Thiemermann et al., "Inhibition of the Activity of Poly(ADP Ribose) Synthetase Reduces Ischemia-Reperfusion Injury in the Heart and Skeletal Muscle", *Proc. Natl. Acad. Sci. USA, 94*:679-83 (1997). This finding has suggested that PARP inhibitors might be able to salvage previously ischemic heart or skeletal muscle tissue.

PARP activation has also been shown to provide an index of damage following neurotoxic insults by glutamate (via NMDA receptor stimulation), reactive oxygen intermediates, amyloid β-protein, n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite N-methyl-4-phenylpyridine (MPP^+), which participate in pathological conditions such as stroke, Alzheimer's disease and Parkinson's disease. Zhang et al., "Poly(ADP-Ribose) Synthetase Activation: An Early Indicator of Neurotoxic DNA Damage", *J. Neurochem.*, *65*:3, 1411-14 (1995). Other studies have continued to explore the role of PARP activation in cerebellar granule cells in vitro and in MPTP neurotoxicity. Cosi et al., "Poly(ADP-Ribose) Polymerase (PARP) Revisited. A New Role for an Old Enzyme: PARP Involvement in Neurodegeneration and PARP Inhibitors as Possible Neuroprotective Agents", *Ann. N. Y. Acad. Sci.*, 825:366-79 (1997); and Cosi et al., "Poly(ADP-Ribose) Polymerase Inhibitors Protect Against MPTP-induced Depletions of Striatal Dopamine and Cortical Noradrenaline in C57B1/6 Mice", *Brain Res.*, *729*:264-69 (1996).

Neural damage following stroke and other neurodegenerative processes is thought to result from a massive release of the excitatory neurotransmitter glutamate, which acts upon the N-methyl-D-aspartate (NMDA) receptors and other subtype receptors. Glutamate serves as the predominate excitatory neurotransmitter in the central nervous system (CNS). Neurons release glutamate in great quantities when they are deprived of oxygen, as may occur during an ischemic brain insult such as a stroke or heart attack. This excess release of glutamate in turn causes over-stimulation (excitotoxicity) of N-methyl-D-aspartate (NMDA), AMPA, Kainate and MGR receptors. When glutamate binds to these receptors, ion channels in the receptors open, permitting flows of ions across their cell membranes, e.g., Ca^{2+} and Na^+ into the cells and K^+ out of the cells. These flows of ions, especially the influx of Ca^{2+}, cause overstimulation of the neurons. The over-stimulated neurons secrete more glutamate, creating a feedback loop or domino effect which ultimately results in cell damage or death via the production of proteases, lipases and free radicals.

Excessive activation of glutamate receptors has been implicated in various neurological diseases and conditions including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Huntington's disease, schizophrenia, chronic pain, ischemia and neuronal loss following hypoxia, hypoglycemia, ischemia, trauma, and nervous insult. Recent studies have also advanced a glutamatergic basis for compulsive disorders, particularly drug dependence. Evidence includes findings in many animal species, as well as, in cerebral cortical cultures treated with glutamate or NMDA, that glutamate receptor antagonists block neural damage following vascular stroke. Dawson et al., "Protection of the Brain from Ischemia", *Cerebrovascular Disease*, 319-25 (H. Hunt Batjer ed., 1997). Attempts to prevent excitotoxicity by blocking NMDA, AMPA, Kainate and MGR receptors have proven difficult because each receptor has multiple sites to which glutamate may bind. Many of the compositions that are effective in blocking the receptors are also toxic to animals. As such, there is no known effective treatment for glutamate abnormalities.

The stimulation of NMDA receptors, in turn, activates the enzyme neuronal nitric oxide synthase (NNOS), which causes the formation of nitric oxide (NO), which more directly mediates neurotoxicity. Protection against NMDA neurotoxicity has occurred following treatment with NOS inhibitors. See Dawson et al., "Nitric Oxide Mediates Glutamate Neurotoxicity in Primary Cortical Cultures", *Proc. Natl. Acad. Sci. USA*, *88*:6368-71 (1991); and Dawson et al., "Mechanisms of Nitric Oxide-mediated Neurotoxicity in Primary Brain Cultures", *J. Neurosci.*, *13*:6, 2651-61 (1993). Protection against NMDA neurotoxicity can also occur in cortical cultures from mice with targeted disruption of NNOS. See Dawson et al., "Resistance to Neurotoxicity in Cortical Cultures from Neuronal Nitric Oxide Synthase-Deficient Mice", *J. Neurosci.*, *16*:8, 2479-87 (1996).

It is known that neural damage following vascular stroke is markedly diminished in animals treated with NOS inhibitors or in mice with NNOS gene disruption. Iadecola, "Bright and

Dark Sides of Nitric Oxide in Ischemic Brain Injury", *Trends Neurosci.*, *20*:3, 132-39 (1997); and Huang et al., "Effects of Cerebral Ischemia in Mice Deficient in Neuronal Nitric Oxide Synthase", *Science, 265*:1883-85 (1994). See also, Beckman et al., "Pathological Implications of Nitric Oxide, Superoxide and Peroxynitrite Formation", *Biochem. Soc. Trans.*, *21*:330-34 (1993). Either NO or peroxynitrite can cause DNA damage, which activates PARP. Further support for this is provided in Szabó et al., "DNA Strand Breakage, Activation of Poly(ADP-Ribose) Synthetase, and Cellular Energy Depletion are Involved in the Cytotoxicity in Macrophages and Smooth Muscle Cells Exposed to Peroxynitrite", *Proc. Natl. Acad. Sci. USA*, *93*:1753-58 (1996).

Zhang et al., U.S. Patent No. 5,587,384 issued December 24, 1996, discusses the use of certain PARP inhibitors, such as benzamide and 1,5-dihydroxy-isoquinoline, to prevent NMDA-mediated neurotoxicity and, thus, treat stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease. However, it is has now been discovered that Zhang et al. may have been in error in classifying neurotoxicity as NMDA-mediated neurotoxicity. Rather, it may have been more appropriate to classify the in vivo neurotoxicity present as glutamate neurotoxicity. See Zhang et al. "Nitric Oxide Activation of Poly(ADP-Ribose) Synthetase in Neurotoxicity", *Science, 263*:687-89 (1994). See also, Cosi et al., Poly(ADP-Ribose)Polymerase Inhibitors Protect Against MPTP-induced Depletions of Striatal Dopamine and Cortical Noradrenaline in C57B1/6 Mice", *Brain Res.*, *729*:264-69 (1996).

It is also known that PARP inhibitors affect DNA repair generally. Cristovao et al., "Effect of a Poly(ADP-Ribose) Polymerase Inhibitor on DNA Breakage and Cytotoxicity Induced by Hydrogen Peroxide and γ-Radiation," *Terato., Carcino., and Muta.*, 16:219-27 (1996), discusses the effect of hydrogen peroxide and γ-radiation on DNA strand breaks in the presence of and in the absence of 3-aminobenzamide, a potent inhibitor of PARP. Cristovao et al. observed a PARP-dependent recovery of DNA strand breaks in leukocytes treated with hydrogen peroxide.

PARP inhibitors have been reported to be effective in radiosensitizing hypoxic tumor cells and effective in preventing tumor cells from recovering from potentially lethal damage of DNA after radiation therapy, presumably by their ability to prevent DNA repair. See U.S. Patent Nos. 5,032,617; 5,215,738; and 5,041,653.

Evidence also exists that PARP inhibitors are useful for treating inflammatory bowel disorders. Salzman et al., "Role of Peroxynitrite and Poly(ADP-Ribose)Synthase Activation Experimental Colitis," *Japanese J. Pharm.*, 75, Supp. I:15 (1997), discusses the ability of PARP inhibitors to prevent or treat colitis. Colitis was induced in rats by intraluminal administration of the hapten trinitrobenzene sulfonic acid in 50% ethanol. Treated rats received 3-aminobenzamide, a specific inhibitor of PARP activity. Inhibition of PARP activity reduced the inflammatory response and restored the morphology and the energetic status of the distal colon. See also, Southan et al., "Spontaneous Rearrangement of Aminoalkylithioureas into Mercaptoalkylguanidines, a Novel Class of Nitric Oxide Synthase Inhibitors with Selectivity Towards the *Inducible Isoform*", *Br. J. Pharm.*, *117:619-32* (1996); and Szabó et al., "Mercaptoethylguanidine and Guanidine Inhibitors of Nitric Oxide Synthase React with Peroxynitrite and Protect Against Peroxynitrite-induced Oxidative Damage", *J. Biol. Chem.*, 272:9030-36 (1997).

Evidence also exists that PARP inhibitors are useful for treating arthritis. Szabó et al., "Protective Effects of an Inhibitor of Poly(ADP-Ribose)Synthetase in Collagen-Induced Arthritis," *Japanese J. Pharm.*, *75*, Supp. I:102 (1997), discusses the ability of PARP inhibitors to prevent or treat collagen-induced arthritis. See also Szabó et al., "DNA Strand Breakage, Activation of Poly(ADP-Ribose)Synthetase, and Cellular Energy Depletion are Involved in the Cytotoxicity in Macrophages and Smooth Muscle Cells Exposed to Peroxynitrite," *Proc. Natl. Acad. Sci. USA*, *93*:1753-58 (March 1996); Bauer et al., "Modification of Growth Related Enzymatic Pathways and Apparent Loss of Tumorigenicity of a ras-transformed Bovine Endothelial Cell Line by Treatment with 5-Iodo-6-amino-1,2-

benzopyrone (INH_2BP)", *Intl. J. Oncol.*, *8*:239-52 (1996); and Hughes et al., "Induction of T Helper Cell Hyporesponsiveness in an Experimental Model of Autoimmunity by Using Nonmitogenic Anti-CD3 Monoclonal Antibody", *J. Immuno.*, *153*:3319-25 (1994).

Further, PARP inhibitors appear to be useful for treating diabetes. Heller et al., "Inactivation of the Poly(ADP-Ribose)Polymerase Gene Affects Oxygen Radical and Nitric Oxide Toxicity in Islet Cells," *J. Biol. Chem.*, *270*:19, 11176-80 (May 1995), discusses the tendency of PARP to deplete cellular NAD+ and induce the death of insulin-producing islet cells. Heller et al. used cells from mice with inactivated PARP genes and found that these mutant cells did not show NAD+ depletion after exposure to DNA-damaging radicals. The mutant cells were also found to be more resistant to the toxicity of NO.

Further still, PARP inhibitors have been shown to be useful for treating endotoxic shock or septic shock. Zingarelli et al., "Protective Effects of Nicotinamide Against Nitric Oxide-Mediated Delayed Vascular Failure in Endotoxic Shock: Potential Involvement of PolyADP Ribosyl Synthetase," *Shock*, 5:258-64 (1996), suggests that inhibition of the DNA repair cycle triggered by poly(ADP ribose) synthetase has protective effects against vascular failure in endotoxic shock. Zingarelli et al. found that nicotinamide protects against delayed, NO-mediated vascular failure in endotoxic shock. Zingarelli et al. also found that the actions of nicotinamide may be related to inhibition of the NO-mediated activation of the energy-consuming DNA repair cycle, triggered by poly(ADP ribose) synthetase. See also, Cuzzocrea, "Role of Peroxynitrite and Activation of Poly(ADP-Ribose) Synthetase in the Vascular Failure Induced by Zymosan-activated Plasma," *Brit. J. Pharm.*, *122*:493-503 (1997).

Yet another known use for PARP inhibitors is treating cancer. Suto et al., "Dihydroisoquinolinones: The Design and Synthesis of a New Series of Potent Inhibitors of Poly(ADP-Ribose) Polymerase", *Anticancer Drug Des.*, 7:107-17 (1991), discloses processes for synthesizing a number of different PARP inhibitors. In addition, Suto et al., U.S. Patent No. 5,177,075, discusses several isoquinolines used for enhancing

the lethal effects of ionizing radiation or chemotherapeutic agents on tumor cells. Weltin et al., "Effect of 6(5*H*)-Phenanthridinone, an Inhibitor of Poly(ADP-ribose) Polymerase, on Cultured Tumor Cells", *Oncol. Res.*, 6:9, 399-403 (1994), discusses the inhibition of PARP activity, reduced proliferation of tumor cells, and a marked synergistic effect when tumor cells are co-treated with an alkylating drug.

Still another use for PARP inhibitors is the treatment of peripheral nerve injuries, and the resultant pathological pain syndrome known as neuropathic pain, such as that induced by chronic constriction injury (CCI) of the common sciatic nerve and in which transsynaptic alteration of spinal cord dorsal horn characterized by hyperchromatosis of cytoplasm and nucleoplasm (so-called "dark" neurons) occurs. See Mao et al., Pain, 72:355-366 (1997).

PARP inhibitors have also been used to extend the lifespan and proliferative capacity of cells including treatment of diseases such as skin aging, Alzheimer's disease, atherosclerosis, osteoarthritis, osteoporosis, muscular dystrophy, degenerative diseases of skeletal muscle involving replicative senescence, age-related macular degeneration, immune senescence, AIDS, and other immune senescence diseases; and to alter gene expression of senescent cells. See WO 98/27975.

Large numbers of known PARP inhibitors have been described in Banasik et al., "Specific Inhibitors of Poly(ADP-Ribose) Synthetase and Mono(ADP-Ribosyl)-Transferase", *J. Biol. Chem.*, *267*:3, 1569-75 (1992), and in Banasik et al., "Inhibitors and Activators of ADP-Ribosylation Reactions", *Molec. Cell. Biochem.*, *138*:185-97 (1994).

However, the approach of using these PARP inhibitors in the ways discussed above has been limited in effect. For example, side effects have been observed with some of the best-known PARP inhibitors, as discussed in Milam et al., "Inhibitors of Poly(Adenosine Diphosphate-Ribose) Synthesis: Effect on Other Metabolic Processes", *Science*, *223*:589-91 (1984). Specifically, the PARP inhibitors 3-aminobenzamide and benzamide not only inhibited the action of PARP but also were

shown to affect cell viability, glucose metabolism, and DNA synthesis. Thus, it was concluded that the usefulness of these PARP inhibitors may be severely restricted by the difficulty of finding a dose that will inhibit the enzyme without producing additional metabolic effects.

Accordingly, there remains a need for compounds that inhibit PARP activity, compositions containing those compounds and methods utilizing those compounds, wherein the compounds produce more potent and reliable effects with fewer side effects, with respect to inhibiting PARP activity and treating the diseases and conditions discussed herein.

Multicyclic oxo-substituted compounds other than the compounds of the invention are known. These include, but are not limited to:

I. 3-(5-Hexynyl)-2,4a,5,6,7,7a-hexahydro-1*H*-cyclopenta[c]-pyridin-1-one, shown in Rougeot et al., "Cyclization Reactions of 2-pentynyl-4-pyrimidinones", *J. Heterocycl. Chem.*, *20*:5, 1407-9 (1983);

II. 2,4a,5,6,7,7a-Hexahydro-3-methyl-1*H*-cyclopenta-[c]pyridin-1-one, shown in Davies et al., "Intramolecular Cycloaddition Reactions of Mono- and Dihydroxy-pyrimidines", *J. Chem. Soc.*, *11*:1293-97 (1978);

III. 2,4a,5,6,7,7a-Hexahydro-3-phenyl-1*H*-cyclopenta-[c]pyridin-1-one, shown in Davies et al., "Intramolecular Cycloaddition Reactions of Mono- and Dihydroxy-pyrimidines", *J. Chem. Soc.*, *11*:1293-97 (1978);

IV. Octahydro-3-methyl-1(2*H*)-isoquinolinone, shown in Ochiai et al., "Polarization of Heterocyclic Rings with Aromatic Character. CXLVII. Reaction of 3-Methyl-5,6,7,8-tetrahydroisoquinoline-2-oxide with Acetic Anhydride", *Itsuu Kenkusho Nempo*, *16*:15-23 (1971);

V. Octahydro-<2>pyrindin-1-one, shown in Granger et al., *Bull. Soc. Chim. Fr.*, 233, (1962);

VI. Octahydro-isocarbostyril, shown in:

(a) Di Maio et al., "Photochemistry of Some N-hydroxy Lactams", *Ric. Sci.*, *38*:3, 231-33 (1968);

(b) Di Maio et al., "The Action of Hyponitrous Acid on

Ketonic Compounds. II. 1-Hydrinadanone", *Gazz. Chim. Ital.*, *91*:1124-32 (1961);

(c) Di Maio et al., "Ring Enlargement: The Schmidt Reaction on 1-hydrindanone", *Gazz. Chim. Ital.*, *91*:1345-51 (1961);

(d) Di Maio et al., "The Behavior of Some Cyclic Hydroxamic Acids at Elevated Temperatures", *Gazz. Chim. Ital.*, *94*:5, 590-94 (1964);

(e) Baer et al., "Cyclizations of Dialdehydes with Nitromethane. XII. Phthalaldehyde", *J. Org. Chem.*, *29*:11, 3180-85 (1964);

(f) Ochiai et al., "Polarization of Aromatic Heterocyclic Compounds. CXX. A New Synthesis of 1-Halo-5,6,7,8-tetrahydroisoquinoline", *Pharm. Bull.*, *5*:289-91 (1957); and

(g) Baer et al., "Synthesis of the Isoquinoline System from *o*-Phthalaldehyde and Nitromethane", *Angew. Chem.*, *76*:1, 50 (1964);

VII. 3,5-Dihydro-1*H*-thieno<3,4-c>quinolin-4-one shown in: (a) White et al., "Quinoline Analogues of *Ortho*-Quinodimethane", *Tetrahedron Letters*, *36*:33, 5983-86 (1995); and

(b) White et al., "Dihydrothiophenes as Precursors to Fused Quinolines, Quinolones and Coumarins via *o*-Quinodimethane Intermediates", *Tetrahedron*, *52*:9, 3117-34 (1996);

VIII. 7 (or 9)-Chloro-1,2,3,5-tetrahydro-4*H*-cyclopenta-[c]quinoline-4-one, 1,2,3,4-tetrahydro-7(or 9)-methyl-4*H*-cyclopenta[c]quinoline-4-one and 1,2,3,5-tetrahydro-4*H*-cyclopenta[c]quinolin-4-one, shown in:

(a) Brown et al., "Reaction of Ethyl 2-Oxocyclopentanecarboxylate with Arylamines. Part I. The Preparation of 2,3-dihydro-α-quinindones (2,3,4,5-tetrahydro-4-oxo-1*H*-cyclopenta[c]quinolines)", *J. Chem. Soc.*, 4295-98 (1961);

(b) 1,2,3,5-Tetrahydro-4*H*-cyclopenta-[c]quinoline-4-one, Reisch, "Chemistry of Natural Substances. VII.

Furoquinoline Derivatives By Condensation of Ethyl 2-Propynyl Malonate with Aromatic Amines", *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, *300*:6, 533-39 (1967);

(c) 1,2,3,5-Tetrahydro-4*H*-cyclopenta-[c]quinoline-4-one, Eisch et al., "Studies on Nonpyridinoid Azaaromatic Systems. 7. Synthesis and Tautomeric Character of Cyclopenta[c]quinoline (benzo[c][2]pyrindine)", *J. Org. Chem.*, *43*:11, 2190-96 (1978);

(d) 1,2,3,5-Tetrahydro-4*H*-cyclopenta-[c]quinoline-4-one, Castan et al., "New Arylpiperazine Derivatives with High Affinity for 5-HT_3 Receptor Sites", *Med. Chem. Res.*, *6*:2, 81-101 (1996);

(e) 1,2,3,5-Tetrahydro-4*H*-cyclopenta-[c]quinoline-4-one, Reid et al., "Reactions of Cyclic Enamines. III. Synthesis of N-Heterocycles from Cycloalkenylamine-isocyanate or -isothiocyanate Adducts", *Ann. Chem.*, *688*:177-88 (1965); and

(f) 1,2,3,5-Tetrahydro-4*H*-cyclopenta[c]quinoline-4-one, Reid et al., "Reactions with Cyclic Enamines. I. Reaction of Cycloalkene-amines with Phenyl Isocyanate and Phenylisothiocyanate", *Ann.*, *673*:132-36 (1964);

IX 2-Hydroxy-3,4-cyclopentenoquinoline, shown in Johnson, "The Synthesis of N-Alkyl-2-Oxocyclopentane-Carboxyamides", *J. Chem. Soc.*, 1624-28 (1958);

X. 1,2,4,6-Tetrahydro-5*H*-thiopyrano[3,4-c]quinoline-5-one, shown in Castan et al., "New Arylpiperazine Derivatives with High Affinity for 5-HT_3 Receptor Sites", *Med. Chem. Soc.*, *6*:2, 81-101 (1996);

XI. 6a,7,8,9,10,10a-Hexahydro-*trans*-6(5*H*)-phenanthridinone, shown in:

(a) Masamune et al., "Condensed Polynuclear Perhydro Compounds Containing Nitrogen. XII. Synthesis and Exhaustive Methylation of 5,6,6a,7,8,9,10,10a-Octahydro-phenanthridines and Related Compounds", *J. Org. Chem.*, *29*:3, 681-85 (1964);

(b) 6a,7,8,9,10,10a-Hexahydro-*cis*(∓)6(5*H*)-

phenanthridinone, Naito et al., "Asymmetric Photocyclization of N-α,β-Unsaturated Acylanilides", *Heterocycles*, *22*:2, 237-40 (1984), along with the (6a*R*-*trans*)- and (6a*S*-*trans*)- stereoisomers of the same compound;

(c) Michailidis et al., "Hexahydrogenated Derivatives of Phenanthridone Obtained by Birch Reaction", *C. R. Acad. Sci.*, *275*:17, 961-64 (1972), with *cis* and *trans* stereoisomers of the same compound;

(d) Ninomiya et al., "Photocyclization of Enamides. V. Photocyclization of α,β-Unsaturated Anilides", *J. Chem. Soc.*, *1*:14, 1747-51 (1974), with *cis* stereoisomer; and

(e) Taylor et al., "Phenanthridine Syntheses Via the Diels-Alder Reaction. A New Route to 6(5)-Phenanthridinone", *J. Am. Chem. Soc.*, *78*:5104-8 (1956);

XII. 7,8,9,10-tetrahydro-65(*H*), as shown in

(a) Masamune et al., "The Synthesis and Exhaustive Methylation of 5,6,7,8,9,10,6a,10a-Octahydrophenanthridines and Related Compounds, *J. Org. Chem.*, *29*:3, 681-85 (1964);

(b) Bailey et al., "Reactions of p-Toluenesulfonyl Azide with Derivatives of Cyclohept- and Cyclooctindole, *J. Chem. Soc.*, *1*:7, 763-70 (1974);

(c) Reid et al., "Reactions of Cyclic Enamines. III. Synthesis of N-Heterocycles from Cycloalkenylamine-isocyanate or -isothiocyanate Adducts", *Ann. Chem.*, *688*:177-88 (1965); and

(d) Reid et al., "Reactions with Cyclic Enamines. I. Reaction of Cycloalkene-amines with Phenyl Isocyanate and Phenylisothiocyanate", *Ann.*, 132-36 (1964); and

XIII. 1,2,3,3a,5,9b-Hexahydro-cyclopenta<c>quinolin-4-one, shown in Blount et al., "Stereoisomerism in Polycyclic Systems. Part VI.", *J. Chem. Soc.*, 1979, 1984 (1929).

1,2,3,5,-Tetrahydrocyclopenta[c]quinolin-4-one, as cited in Castan et al., "New Arylpiperazine Derivatives with High

Affinity for 5-HT_3 Receptor Sites", *Med. Chem. Res.*, *6*:2, 81-101 (1996), is an intermediate in the preparation of new arylpiperazine derivatives with high affinity for serotoninergic S_3 receptor sites in relation to structure. However, it is not believed that this intermediate or any of the previously cited oxo-substituted compounds have been shown to inhibit PARP activity.

Other oxo-substituted compounds are disclosed in:

(1) Taylor et al., "Phenanthridine Syntheses Via the Diels-Alder Reaction. A New Route to 6(5)-Phenanthridinone", *J. Am. Chem. Soc.*, *78*:5104-8 (1956);

(2) Reid et al., "Reactions of Cyclic Enamines. III. Synthesis of N-Heterocycles from Cycloalkenylamine-isocyanate or -isothiocyanate Adducts", *Ann. Chem.*, *688*:177-88 (1965);

(3) Gauthier, U.S. Patent No. 3,838,134, disclosing phenanthridinones used as antiviral agents; and

(4) Winter et al., U.S. Patent No. 4,382,943, disclosing anti-allergic aryl ether derivatives.

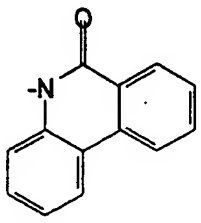
It is not believed that any of these oxo-substituted compounds have been shown to inhibit PARP activity.

Other structurally distinguishable compounds have been disclosed for medical treatments and other uses. For example, Winter et al., U.S. Patent No. 4,382,943, discloses the use of dibenzo-[b][d]pyran-6-one as an antihistamine, an anti-oedematous agent and an antiphlogistic agent. Meyer et al., U.S. Patent No. 4,169,897, entitled "2,7-Bis-Basic Ethers of 9-Phenanthrol and 9-Loweralkoxy Phenanthrol", discloses certain phenanthrenes and phenanthrinidinones useful for preventing or inhibiting viral infections.

Hunger et al, U.S. Patent No. 4,082,741, entitled "Disazo Pigments Derived from 3,8-Diamino-Phenanthridone-(10)", discloses compounds useful for pigments suitable for preparing of printing inks, color lacquers and dispersion paints, which are used to dye rubber, plastic materials, and natural or synthetic resins. Montgomery, U.S. Patent No. 3,291,801, discloses octahydro-6(5)-phenanthridinones that may be converted to the corresponding 6(5)-phenanthridinones, which are useful as intermediates for forming therapeutically active

compounds. Hegar, U.S. Patent No. 3,507,872, entitled "Indolyl-Quinolinium Dyestuffs", discloses water soluble basic dyestuffs comprising α-pyridones or γ-pyridones.

Schohe et al., U.S. Patent No. 5,274,097 discloses a number of 1,3-di-substituted pyrrolidines, which can be substituted with, among many others, the following radical:



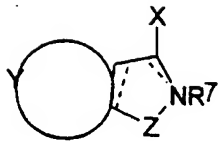
These structures are said to have high affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT_1 type, which are said to combat diseases distinguished by disturbances of the serotoninergic system, in particular, those involved with receptors having a high affinity for 5-hydroxytryptamine (5-HT_1) type.

The inventors have now discovered that selected oxo-substituted PARP inhibitors can treat or prevent tissue damage resulting from cell damage or death due to necrosis or apoptosis and can ameliorate neural tissue damage, including that following focal ischemia and reperfusion injury. Generally, inhibition of PARP activity spares the cell from energy loss, preventing irreversible depolarization of the neurons and, thus, provides neuroprotection. While not wishing to be bound thereby, it is thought that PARP activation may play a common role in still other excitotoxic mechanisms, perhaps as yet undiscovered, in addition to the production of free radicals and NO.

SUMMARY OF THE INVENTION

The present invention is directed to a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring

members;

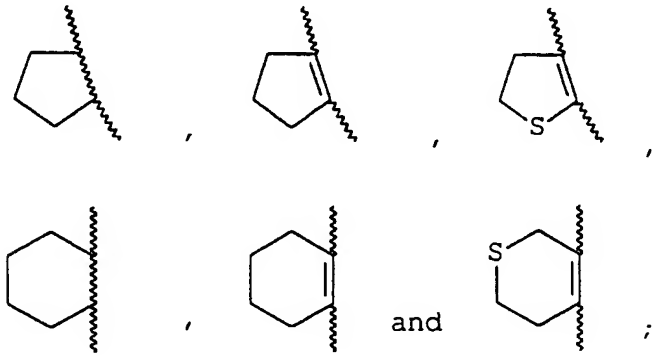
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

with the provisos that:

(a) when X is double-bonded oxygen, and Z is $-CHR^2CHR^3-$, R^3 cannot be hydrogen or methyl;

(b) when X is double-bonded oxygen, and Z is $-R^6C=CR^3-$, R^3 cannot be methyl, phenyl, or $-(CH_2)_4-C\equiv CH$;

(c) when R^3 and R^6 are taken together to form a fused aromatic ring, Y cannot be a ring selected from the group consisting of:



(d) when X, Y and Z, taken together, form a phenanthridone, a phenanthridinone, a phenanthrene, or a phenanthridine nucleus with an amino group or an aminoalkoxylene group in the 3-position, the 8-position cannot also be substituted with an amino group or an aminoalkoxylene group; and

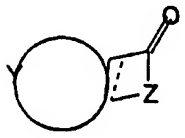
(e) when X is a double bonded oxygen, and Z is a 6-membered unsaturated ring, and Y is phenyl, then the 2-position of the Z-ring cannot be substituted with a hydrogen or a nitro group;

(f) when X is -OH or double bonded oxygen, and Z is -CH=CH-, then Y is not phenyl or 5-hydroxyphenyl;

(g) when X is a double bonded oxygen, and Z is -CH=N-, then Y is not phenyl; or

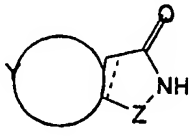
(h) when X is a double bonded oxygen, and Z is -C(O)NH-, then Y is not aminophenyl.

In another embodiment, a process for making the compound of formula I comprises the step of contacting an intermediate of formula IV:



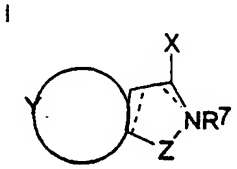
IV

wherein Y and Z are as defined above, with a nitrogen-insertion agent to form a compound of formula V:



V

In yet another embodiment, the pharmaceutical composition of the invention comprises a pharmaceutically acceptable carrier and a compound of formula I containing at least one ring nitrogen:



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and

R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

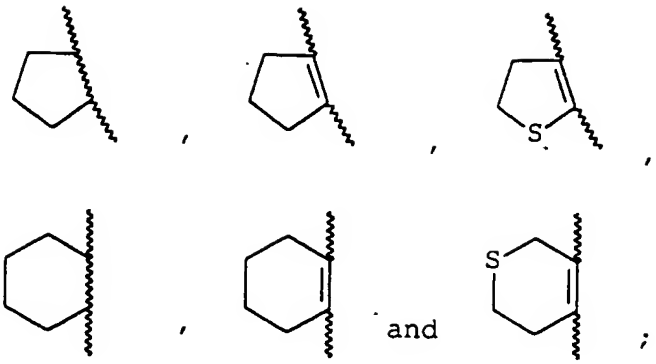
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

with the provisos that:

(a) when X is double-bonded oxygen, and Z is $-CHR^2CHR^3-$, R^3 cannot be hydrogen or methyl;

(b) when X is double-bonded oxygen, and Z is $-R^6C=CR^3-$, R^3 cannot be methyl, phenyl, or $-(CH_2)_4-C\equiv CH$;

(c) when R^3 and R^6 are taken together to form a fused aromatic ring, Y cannot be a ring selected from the group consisting of:



(d) when X, Y and Z, taken together, form a phenanthridone, a phenanthridinone, a phenanthrene, or a phenanthridine nucleus with an amino group or an aminoalkoxylene group in the 3-position, the 8-position cannot also be substituted with an amino group or an aminoalkoxylene group; and

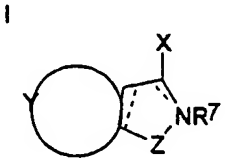
(e) when X is a double bonded oxygen, and Z is a 6-membered unsaturated ring, and Y is phenyl, then the 2-position of the Z-ring cannot be substituted with a hydrogen or a nitro group;

(f) when X is -OH or double bonded oxygen, and Z is -CH=CH-, then Y is not phenyl or 5-hydroxyphenyl;

(g) when X is a double bonded oxygen, and Z is -CH=N-, then Y is not phenyl; or

(h) when X is a double bonded oxygen, and Z is -C(O)NH-, then Y is not aminophenyl.

In a still further embodiment of the invention, the pharmaceutical composition of the invention comprises a pharmaceutically acceptable carrier and a compound of formula I containing at least one ring nitrogen:



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino; and wherein the compound of formula I is present in an amount that is sufficient to inhibit PARP activity, to treat or prevent tissue damage resulting from cell damage or death due to

necrosis or apoptosis, to effect a neuronal activity not mediated by NMDA toxicity, to effect a neuronal activity mediated by NMDA toxicity, to treat neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; to prevent or treat vascular stroke; to treat or prevent cardiovascular disorders; to treat other conditions and/or disorders such as age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (such as colitis and Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic and/or acute pain (such as neuropathic pain), renal failure, retinal ischemia, septic shock (such as endotoxic shock), and skin aging; to extend the lifespan and proliferative capacity of cells; to alter gene expression of senescent cells; or to radiosensitize hypoxic tumor cells.

In an additional embodiment, a method of inhibiting PARP activity comprises administering a compound of formula I, as described above for the pharmaceutical compositions of the invention. In yet further embodiments, the amount of the compound administered in the methods of the invention is sufficient for treating tissue damage resulting from cell damage or death due to necrosis or apoptosis, neural tissue damage resulting from ischemia and reperfusion injury, or neurological disorders and neurodegenerative diseases; to prevent or treat vascular stroke; to treat or prevent cardiovascular disorders; to treat other conditions and/or disorders such as age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (such as colitis and Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic and/or acute pain (such as neuropathic pain), renal failure, retinal ischemia, septic shock (such as endotoxic shock), and skin aging; to extend the lifespan and proliferative capacity of cells; to alter gene expression of

senescent cells; or to radiosensitize hypoxic tumor cells.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the distribution of the cross-sectional infarct area at representative levels along the rostrocaudal axis, as measured from the interaural line in non-treated animals and in animals treated with 10 mg/kg of 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone.

Figure 2 shows the effect of intraperitoneal administration of 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone on the infarct volume.

DETAILED DESCRIPTION OF THE INVENTION

Oxo-substituted Compounds

The oxo-substituted compounds of the present invention often act as PARP inhibitors. As such, they may treat or prevent neural tissue damage resulting from cell damage or death due to necrosis or apoptosis, cerebral ischemia and reperfusion injury or neurodegenerative diseases in an animal; they may extend the lifespan and proliferative capacity of cells and thus be used to treat or prevent diseases associated therewith; they may alter gene expression of senescent cells; and they may radiosensitize hypoxic tumor cells. Preferably, the oxo-substituted compounds of the invention treat or prevent tissue damage resulting from cell damage or death due to necrosis or apoptosis, and/or effect neuronal activity, either mediated or not mediated by NMDA toxicity. These oxo-substituted compounds are thought to interfere with more than the glutamate neurotoxicity and NO-mediated biological pathways. Further, the oxo-substituted compounds of the invention can treat or prevent other tissue damage related to PARP activation.

For example, the oxo-substituted compounds of the invention can treat or prevent cardiovascular tissue damage resulting from cardiac ischemia or reperfusion injury. Reperfusion injury, for instance, occurs at the termination of cardiac bypass procedures or during cardiac arrest when the heart, once prevented from receiving blood, begins to reperfuse.

The oxo-substituted compounds of the present invention can also be used to extend or increase the lifespan or proliferation of cells and thus to treat or prevent diseases associated therewith and induced or exacerbated by cellular senescence including skin aging, atherosclerosis, osteoarthritis, osteoporosis, muscular dystrophy, degenerative diseases of skeletal muscle involving replicative senescence, age-related macular degeneration, immune senescence, AIDS and other immune senescence diseases, and other diseases associated with cellular senescence and aging, as well as to alter the gene expression of senescent cells. These compounds can also be used to treat cancer and to radiosensitize hypoxic tumor cells to render the tumor cells more susceptible to radiation therapy and to prevent the tumor cells from recovering from potentially lethal damage of DNA after radiation therapy, presumably by their ability to prevent DNA repair. The compounds of the present invention can be used to prevent or treat vascular stroke; to treat or prevent cardiovascular disorders; to treat other conditions and/or disorders such as age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (such as colitis and Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic and/or acute pain (such as neuropathic pain), renal failure, retinal ischemia, septic shock (such as endotoxic shock), and skin aging.

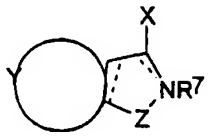
The oxo-substituted compounds of the invention can treat or prevent other tissue damage that can occur related to PARP activation. These compounds are thought to interfere with more than the glutamate neurotoxicity and NO-mediated biological pathways. Preferably, the oxo-substituted compounds of the invention exhibit an IC_{50} for inhibiting PARP *in vitro* of about 100 uM or lower, more preferably, about 25 uM or lower. Preferably, the oxo-substituted compounds of the invention effect a neuronal activity not mediated by NMDA

Preferably, the compounds of the invention act as PARP inhibitors to treat or prevent tissue damage resulting from

cell death or damage due to necrosis or apoptosis; to treat or prevent neural tissue damage resulting from cerebral ischemia and reperfusion injury or neurodegenerative diseases in an animal; to extend or increase the lifespan or proliferation of cells and thus to treat or prevent diseases associated therewith and induced or exacerbated by cellular senescence including skin aging, atherosclerosis, osteoarthritis, osteoporosis, muscular dystrophy, degenerative diseases of skeletal muscle involving replicative senescence, age-related macular degeneration, immune senescence, AIDS and other immune senescence diseases, and other diseases associated with cellular senescence and aging, as well as to alter the gene expression of senescent cells. These compounds can also be used to treat cancer and to radiosensitize hypoxic tumor cells to render the tumor cells more susceptible to radiation therapy and to prevent the tumor cells from recovering from potentially lethal damage of DNA after radiation therapy, presumably by their ability to prevent DNA repair. They may also be used to treat or prevent chronic pain, acute pain, neuropathic pain, renal failure, cachexia, or retinal ischemia.. These compounds are thought to interfere with more than the NMDA-neurotoxicity and NO-mediated biological pathways. Preferably, the compounds of the invention exhibit an IC_{50} for inhibiting PARP in vitro of about 100 uM or lower, more preferably, about 25 uM or lower.

The compound of the present invention has the formula:

I



wherein X is double-bonded oxygen or -OH. In a particularly preferred embodiment, X is double-bonded oxygen.

When R^7 is present, it is hydrogen or lower alkyl. Examples of useful lower alkyl groups for R^7 include, without limitation, methyl, ethyl, isopropyl, tert-butyl, n-pentyl, and n-hexyl. Preferably, however, R^7 is hydrogen.

Y in formula I represents the atoms necessary to form a fused 5- or 6-membered, or aromatic or non-aromatic carbocyclic or heterocyclic ring. Carbocyclic moieties include alicyclic

and aromatic structures. When Y forms a fused 5-membered carbocyclic ring, examples include a cyclopentane, cyclopentene or cyclopentadiene fused nucleus. When Y forms a 5-membered heterocyclic ring, examples include a fused pyrrole, isopyrrole, imidazole, isoimidazole, pyrazole, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, isothiazole, isoxazole, furazan, furan, thiophene, 1,2,3-triazole, 1,2,4-triazole, dithiole, oxathiole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, and the like ring structures.

When Y forms a 6-membered carbocyclic ring, examples include a fused cyclohexane, cyclohexene or benzene nucleus, optionally substituted with additional fused rings, thus forming, for example, naphthalene, anthracene, phenanthrene, benzonaphthene, and the like ring systems. When Y forms a 6-membered heterocyclic ring, examples include a pyridine, pyrazine, pyrimidine, pyridazine, pyran, pyrone, dioxin, piperidine, piperazine, morpholine, triazine, oxazine, isoxazine, oxathiazine, oxadiazine, and the like rings.

In a preferred embodiment, however, Y has at least one site of unsaturation. Even more preferably, Y represents the atoms necessary to form a fused benzene or naphthalene ring. Y may be unsubstituted or substituted with a non-hydrogen non-interfering substituent.

Possible substituents of Y include any substituent that does not interfere with the reactions and purposes of the invention. Examples include, without limitation, straight or branched chain alkyl groups, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, tert-butyl, n-pentyl, 2-methylpentyl, 2-methylhexyl, dodecyl, octadecyl and the like; straight or branched chain alkenyl groups, such as ethenyl, propenyl, butenyl, pentenyl, 2-methylpentenyl, vinyl, isopropenyl, 2,2-dimethyl-1-propenyl, decenyl, hexadecenyl and the like; straight or branched chain alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and the like; cycloalkyl groups, such as cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like; cycloalkenyl groups, such as cyclopropenyl, cyclopentadienyl, cyclohexenyl, cyclooctenyl and

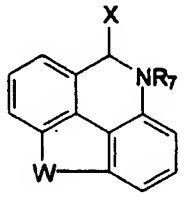
the like; aralkyl groups, such as benzyl, 3-(1)-naphthyl-1-propyl, p-halobenzyl, p-ethylbenzyl, 1-phenyl-1-propyl, 3-pyridinyl-1-propyl, 1-phenyl-2-sec-butyl, 4-phenyl-4-methyl-1-pentyl and the like; aryl groups such as phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzamidazolyl, benzathiazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like; alkoxy groups such as methoxy, ethoxy, sec-propoxy, tert-butoxy, pentoxy, nonoxy and the like; alkenoxy, such as ethenoxy, 2-propenoxy, 3-butenoxy, 2,2-dimethyl-3-butenoxy, 1-hexenoxy, 3-octenoxy, 2-nonenoxy and the like; aryloxy, such as phenoxy, naphthoxy, pyridinoxy and the like; aralkyloxy groups, such as benzyloxy, 1-naphthyl-2-ethoxy and the like; alkanoyl groups such as formyl, acetyl, propanoyl, butanoyl, pentanoyl, benzoyl and the like; haloalkyl groups, such as trifluoromethyl; non-aromatic heterocyclic groups; and other groups, such as hydroxy, carboxy, carbonyl, amino, alklyamino, amido, cyano, isocyano, nitro, nitroso, nitrilo, isonitrilo, imino, azo, diazo, sulfonyl, sulfoxy, SO_3K, thio, thiocarbonyl, alklythio, sulfhydryl, halo and the like.

Possible substituents on the above-described aryl groups can be any non-interfering substituent. However, preferred substituents include, without limitation, alkyl, alkenyl, alkoxy, phenoxy, benzyloxy, cycloalkyl, cycloalkenyl, hydroxy, carboxy, carbonyl, amino, amido, cyano, isocyano, nitro, nitroso, nitrilo, isonitrilo, imino, azo, diazo, sulfonyl, sulfoxy, thio, thiocarbonyl, sulfhydryl, halo, haloalkyl, and aryl.

Preferably, when Y is substituted with a non-hydrogen, non-interfering substituent, the substituent is selected from

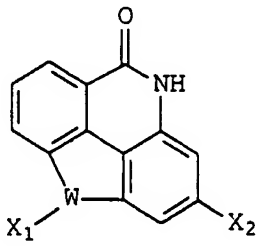
the group consisting of $-NO_2$, halo such as chloro or bromo, $-OR^1$ or $-NHR^1$, where R^1 is hydrogen or lower alkyl.

In another preferred embodiment, Y is optionally substituted with a non-interfering substituent that bridges two or more of the fused rings of the compound. Such a compound may have, for example, a tetracyclic structure of the formula:



where W is -O-, -S-, $-NR^1$, -CHO, -CHOH, or $-CHNH_2$ where R^1 is hydrogen or lower alkyl. Preferably, R^1 is lower alkyl, as described above.

An especially preferred embodiment is where the compound has a tetracyclic bridging structure to ring Y, having the formula:



where W is -CH-; X_1 is hydrogen, hydroxy, or amino; and X_2 is hydrogen, amino, 1-piperidine, 1-piperazine, 1-imidazolidine, or hydroxy.

In yet another embodiment, Y can be substituted with two or more non-hydrogen substituents which, taken together, themselves form an additional fused 5- or 6-membered ring, such as a fused cyclopentyl, cyclopentadiene, benzene, cyclohexene, or cyclohexane ring.

Z in formula I can be

(i) $-CHR^2CHR^3-$;

(ii) $-R^6C=CR^3-$;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen.

Preferably, Z is $-CHR^2CHR^3-$, $-R^6C=CR^3-$ or $-R^2C=N-$.

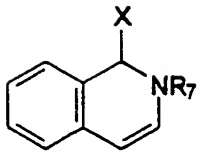
When Z is $-CHR^2CHR^3-$, R^2 is in the meta-position and R^3 is in the ortho-position relative to the ring nitrogen of formula I. When Z is $-R^6C=CR^3-$, R^6 is meta to the ring nitrogen.

R^2,R^3,R^9 and R^{10} in formulas (i) - (vi) above can be, independently, hydrogen; hydroxy, amino, dimethylamino, nitro,; alkyl, such as methyl, ethyl, isopropyl, tert-butyl, n-pentyl, sec-octyl, dodecyl and the like; aryl, such as phenyl, piperidine, piperazine, and imidazolidine,; or aralkyl, such as benzyl, 1-naphthylmethyl, and p-halo benzyl.

In formula (ii) ($-R^6C=CR^3-$), R^6 and R^3, independently can be hydrogen, hydroxy, alkylamino, dimethylamino, lower alkyl as described above, aryl as described above, aralkyl as described above, halo such as chlorine and bromine, $-NO_2$, $-COOR^7$ or $-NR^7R^8$. When R^3 is $-NR^7R^8$, R^8 is independently hydrogen or C_1-C_9 alkyl. Examples of useful C_1-C_9 alkyl groups for R^8 include, without limitation, methyl, ethyl, isopropyl, tert-butyl, n-pentyl, n-hexyl, heptenyl, sec-octyl, and nonyl. Preferably, however, R^8 is lower alkyl as described above.

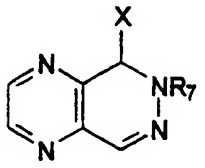
Alternatively, R^3 and R^6, taken together, can form a fused aromatic, mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms. Examples of such rings include a fused pyrrole, isopyrrole, imidazole, isoimidazole, triazole, pyrazole, pyridine, thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, benzene, naphthalene, acridine, pyran, pyrone, pyrazine, pyrimidine, pyridazine, or triazine groups. When Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused aromatic ring, the ring formed is preferably substituted with one or more non-hydrogen non-interfering substituents, as described above for Y. Particularly preferred substituents are selected from the group consisting of halo such as chloro and bromo, amino and nitro.

In the compound of the invention, the multicyclic nuclear ring structure formed by Y and Z is preferably one of the following:

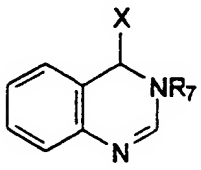


1,2-dihydro-isoquinoline

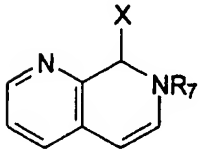
1,2-dihydro-phthalazine



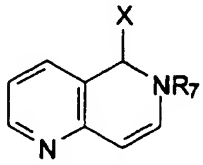
3,4-dihydro-pteridine



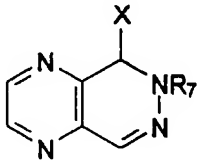
3,4-dihydro-quinazoline



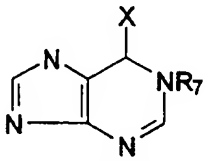
1,2-dihydro-pyrido[3,4b]pyridine



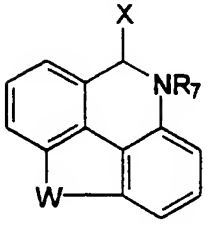
1,2-dihydro-pyrido[4,3b]pyridine



1,2-dihydro-pyrazino[2,3d]pyridazine

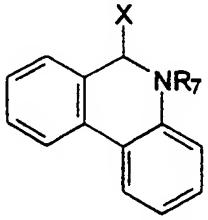


1,6-dihydro-purine



bridging structure

and



5,6-dihydro-phenanthridine

wherein W is as defined as above, or the pharmacologically acceptable base or acid addition salts, prodrug, metabolite, stereoisomer, or mixtures thereof. Preferably, the compound of formula I has an isoquinoline, pteridine, phenanthridine, phthalazine, quinazoline nucleus or the tetracyclic bridging

structure shown above. Most preferably, the compound has a phenanthridine nucleus.

The following specific examples of oxo-substituted compounds of formula I, as shown below in TABLE I, are illustrative of useful embodiments of the invention and are not to be construed as limiting the invention thereto.

I

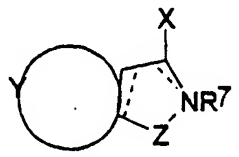
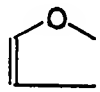
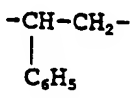
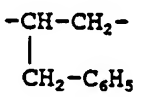
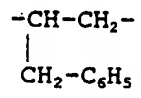
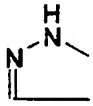
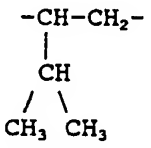
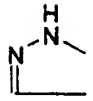
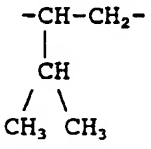
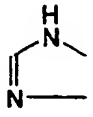
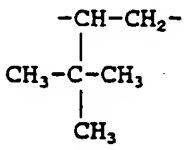
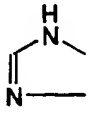
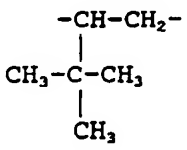
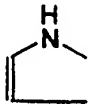
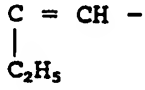
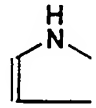
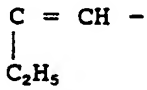
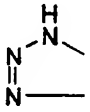
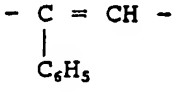
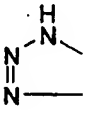
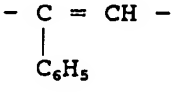
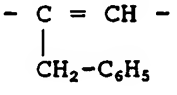
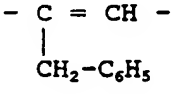
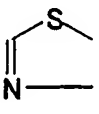
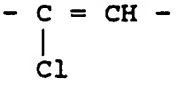
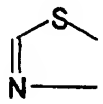
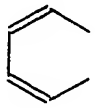
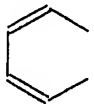
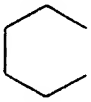
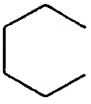
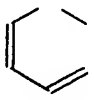
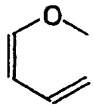


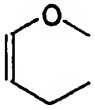
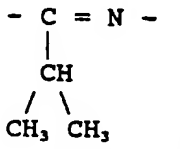
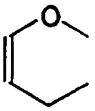
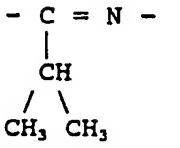
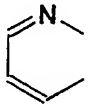
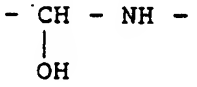
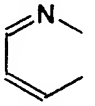
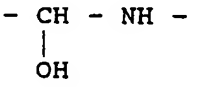
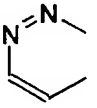
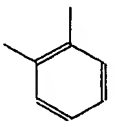
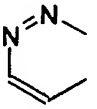
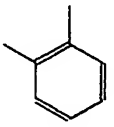
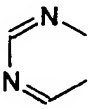
TABLE I

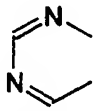
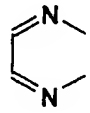
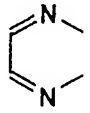
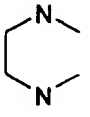
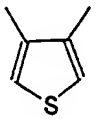
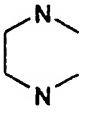
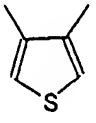
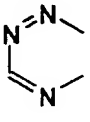
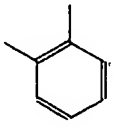
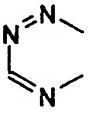
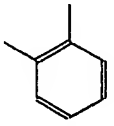
Compound No.	X	Y	Z
1	OH		$-CH_2-CH_2-$
2	O		$-CH-CH_2-$ CH_3
3	OH		$-CH-CH_2-$ CH_3
4	O	O	$-CH-CH_2-$ C_6H_5

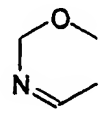
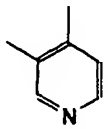
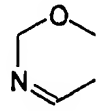
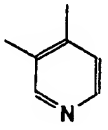
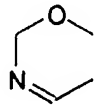
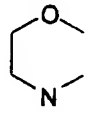
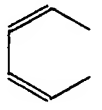
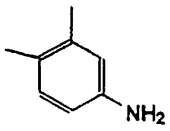
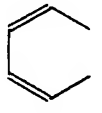
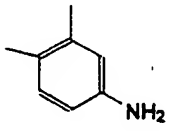
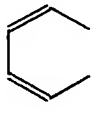
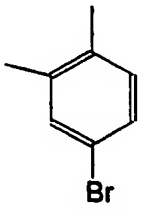
Compound No.	X	Y	Z
5			
6			
7			
8			
9			
10			
11			

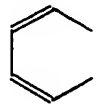
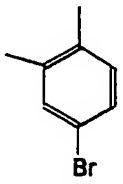
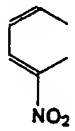
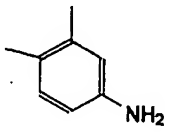
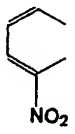
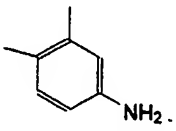
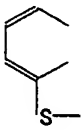
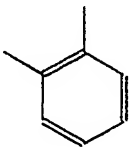
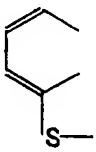
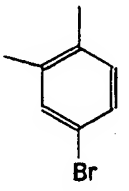
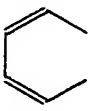
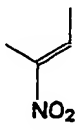
Compound No.	X	Y	Z
12			
13			
14			
15			
16			
17			
18			

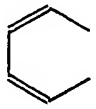
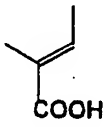
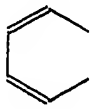
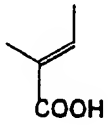
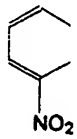
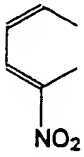
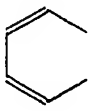
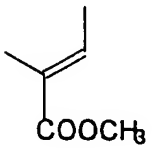
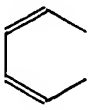
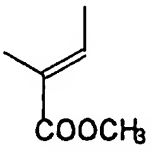
Compound No.	X	Y	Z
19	OH		- C = CH - Cl
20	O		- C = CH - Br
21	OH		- C = CH - Br
22	O		- C = CH - NH-C_2H_5
23	OH		- C = CH - NH-C_2H_5
24	O		- CH_2 = N -
25	OH		- CH_2 = N -

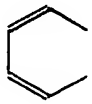
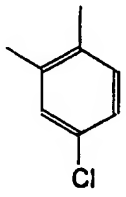
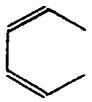
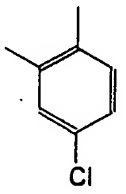
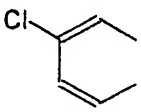
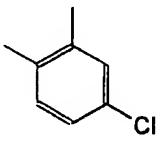
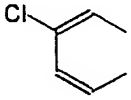
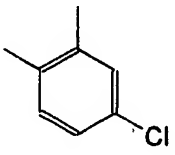
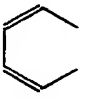
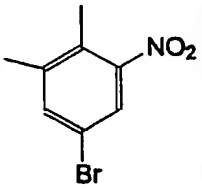
Compound No.	X	Y	Z
26			
27			
28			
29			
30			
31			
32			- CO - NH -

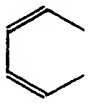
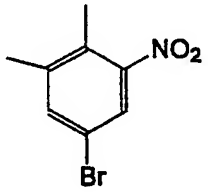
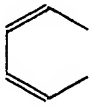
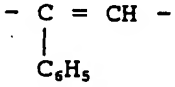
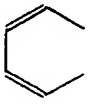
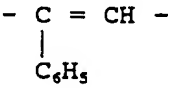
Compound No.	X	Y	Z
33			- CO - NH -
34			- CO - N - C_2H_5
35			- CO - N - C_2H_5
36			
37			
38			
39			

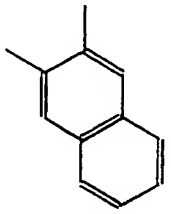
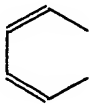
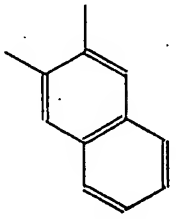
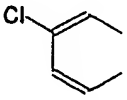
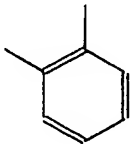
Compound No.	X	Y	Z
40			
41			
42			- CH_2 - CH_2 -
43			- CH_2 - CH_2 -
44			
45			
46			

Compound No.	X	Y	Z
47			
48			
49			
50			
51			
52			

Compound No.	X	Y	Z
53			
54			
55			
56			
57			
58			

Compound No.	X	Y	Z
59			
60			
61			
62			
63			

Compound No.	X	Y	Z
64			
65			
66			
67			- CH = CH -
68			- CH = CH -

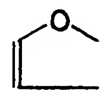
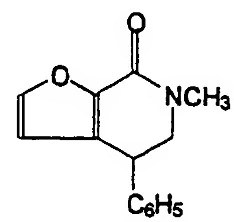
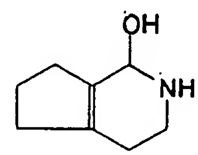
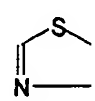
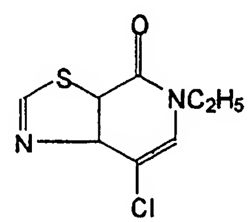
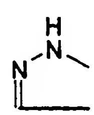
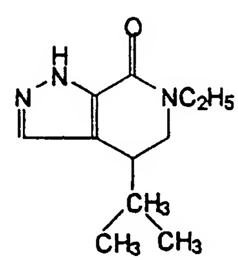
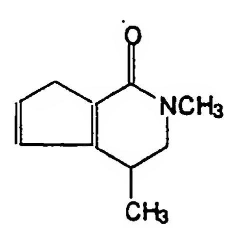
Compound No.	X	Y	Z
69			
70			
71			

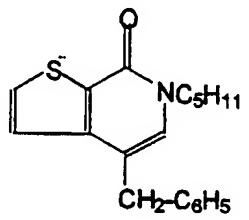
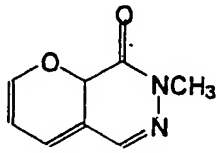
Also included are the pharmacologically acceptable base or acid addition salts, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof.

Particularly preferred compounds of TABLE I of the invention are Compounds Nos. 46, 48, 50, 52, 59, 61, 63, 69 and 71. Most preferably, of this group, the compound of the invention is Compound No. 59.

Another preferred group of compounds of formula I is as shown below in TABLE II:

TABLE II

X	Y	Z	Compound Structure
		$-CH-CH_2-$ | C_6H_5	
		$-CH_2-CH_2-$	
		$-C=CH-$ | Cl	
		$-CH-CH_2-$ | CH / \\ CH_3 CH_3	
		$-CH-CH_2-$ | CH_3	

X	Y	Z	Compound Structure
O	S	-C=CH- $CH_2-C_6H_5$	
O	O	$-CH_2=N-$	

Another example of a preferred class of compounds as is shown below in TABLE III:

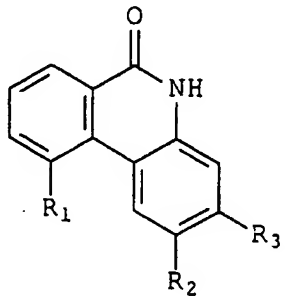


TABLE III

R_1	R_2	R_3
CH_3	Cl	F
CH_3	H	F
CH_3	NO_2	F
NH_2	Cl	F
NH_2	NO_2	F
NH_2	Cl	H
NH_2	Cl	NO_2
NH_2	H	F

NH_2	H	NO_2
NH_2	CH_3	H
NO_2	H	F
NO_2	NO_2	F
OH	Cl	F
OH	NO_2	F
Br	H	F
Br	NO_2	H

Another example of a preferred class of compounds as is shown below in TABLE IV:

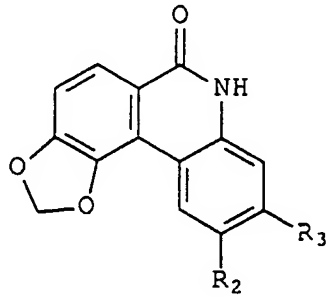


TABLE IV

R_2	R_3
Cl	H
H	F
H	NO_2

Another example of a preferred class of compounds as is shown below in TABLE V:

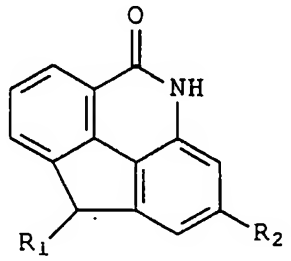


TABLE V

R_1	R_2
H	H
H	NH_2
H	1-piperidine
H	1-piperazine
H	1-imidazolidine
H	OH
OH	H
OH	NH_2
OH	1-piperidine
OH	1-piperazine
OH	1-imidazolidine
OH	OH
NH_2	H
NH_2	NH_2
NH_2	1-piperidine
NH_2	1-piperazine
NH_2	1-imidazolidine
NH_2	OH

Compounds of the present invention may possess one or more asymmetric center(s) and thus can be produced as mixtures (racemic and non-racemic) of stereoisomers, or as individual R- and S- stereoisomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of synthesis, or by resolving a compound of formula I.

The term "isomers" refer to compounds having the same number and kind of atoms, and hence, the same molecular weight, but differing in respect to the arrangement or configuration of the atoms. "Stereoisomers" are isomers that differ only in the arrangement of atoms in space. "Enantiomers" are a pair of

stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal or roughly equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

The compounds of the invention may be useful in a free base form, in the form of pharmaceutically acceptable salts, pharmaceutically acceptable hydrates, pharmaceutically acceptable esters, pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable metabolites, and in the form of pharmaceutically acceptable stereoisomers. These forms are all within the scope of the invention. In practice, the use of these forms amounts to use of the neutral compound.

"Pharmaceutically acceptable salt", "hydrate", "ester" or "solvate" refers to a salt, hydrate, ester, or solvate of the inventive compounds which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. Organic acids can be used to produce salts, hydrates, esters, or solvates such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, p-toluenesulfonate, bisulfate, sulfamate, sulfate, naphthylate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentane-propionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate heptanoate, hexanoate, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, tosylate and undecanoate. Inorganic acids can be used to produce salts, hydrates, esters, or solvates such as hydro-chloride, hydrobromide, hydroiodide, and thiocyanate.

Examples of suitable base salts, hydrates, esters, or solvates include hydroxides, carbonates, and bicarbonates of ammonia, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, and zinc salts.

Salts, hydrates, esters, or solvates may also be formed with organic bases. Organic bases suitable for the formation of pharmaceutically acceptable base addition salts, hydrates,

esters, or solvates of the compounds of the present invention include those that are non-toxic and strong enough to form such salts, hydrates, esters, or solvates. For purposes of illustration, the class of such organic bases may include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, triethylamine and dicyclohexylamine; mono-, di- or trihydroxyalkylamines, such as mono-, di-, and triethanolamine; amino acids, such as arginine and lysine; guanidine; N-methyl-glucosamine; N-methyl-glucamine; L-glutamine; N-methyl-piperazine; morpholine; ethylenediamine; N-benzyl-phenethylamine; (trihydroxy-methyl)aminoethane; and the like. See, for example, "Pharmaceutical Salts," *J. Pharm. Sci.*, *66*:1, 1-19 (1977). Accordingly, basic nitrogen-containing groups can be quaternized with agents including: lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides such as benzyl and phenethyl bromides.

The acid addition salts, hydrates, esters, or solvates of the basic compounds may be prepared either by dissolving the free base of a PARP inhibitor in an aqueous or an aqueous alcohol solution or other suitable solvent containing the appropriate acid or base, and isolating the salt by evaporating the solution. Alternatively, the free base of the PARP inhibitor may be reacted with an acid, as well as reacting the PARP inhibitor having an acid group thereon with a base, such that the reactions are in an organic solvent, in which case the salt separates directly or can be obtained by concentrating the solution.

"Pharmaceutically acceptable prodrug" refers to a derivative of the inventive compounds which undergoes biotransformation prior to exhibiting its pharmacological effect(s). The prodrug is formulated with the objective(s) of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g.,

increased hydrosolubility), and/or decreased side effects (e.g., toxicity). The prodrug can be readily prepared from the inventive compounds using methods known in the art, such as those described by *Burger's Medicinal Chemistry and Drug Chemistry*, Fifth Ed., Vol. 1, pp. 172-178, 949-982 (1995). For example, the inventive compounds can be transformed into prodrugs by converting one or more of the hydroxy or carboxy groups into esters.

"Pharmaceutically acceptable metabolite" refers to drugs that have undergone a metabolic transformation. After entry into the body, most drugs are substrates for chemical reactions that may change their physical properties and biologic effects. These metabolic conversions, which usually affect the polarity of the compound, alter the way in which drugs are distributed in and excreted from the body. However, in some cases, metabolism of a drug is required for therapeutic effect. For example, anticancer drugs of the antimetabolite class must be converted to their active forms after they have been transported into a cancer cell. Since must drugs undergo metabolic transformation of some kind, the biochemical reactions that play a role in drug metabolism may be numerous and diverse. The main site of drug metabolism is the liver, although other tissues may also participate.

A feature characteristic of many of these transformations is that the metabolic products are more polar than the parent drugs, although a polar drug does sometimes yield a less polar product. Substances with high lipid/water partition coefficients, which pass easily across membranes, also diffuse back readily from tubular urine through the renal tubular cells into the plasma. Thus, such substances tend to have a low renal clearance and a long persistence in the body. If a drug is metabolized to a more polar compound, one with a lower partition coefficient, its tubular reabsorption will be greatly reduced. Moreover, the specific secretory mechanisms for anions and cations in the proximal renal tubules and in the parenchymal liver cells operate upon highly polar substances.

As a specific example, phenacetin (acetophenetidin) and acetanilide are both mild analgesic and antipyretic agents, but

are transformed within the body to a more polar and more effective metabolite, p-hydroxyacetanilid (acetaminophen), which is widely used today. When a dose of acetanilid is given to a person, the successive metabolites peak and decay in the plasma sequentially. During the first hour, acetanilid is the principal plasma component. In the second hour, as the acetanilid level falls, the metabolite acetaminophen concentration reaches a peak. Finally, after a few hours, the principal plasma component is a further metabolite that is inert and can be excreted from the body. Thus, the plasma concentrations of one or more metabolites, as well as the drug itself, can be pharmacologically important.

The reactions involved in drug metabolism are often classified into two groups, as shown in the TABLE VI. Phase I (or functionalization) reactions generally consist of (1) oxidative and reductive reactions that alter and create new functional groups and (2) hydrolytic reactions that cleave esters and amides to release masked functional groups. These changes are usually in the direction of increased polarity.

Phase II reactions are conjugation reactions in which the drug, or often a metabolite of the drug, is coupled to an endogenous substrate, such as glucuronic acid, acetic acid, or sulfuric acid.

TABLE VI

Phase I Reactions (functionalization reactions):

(1) Oxidation via the hepatic microsomal P450 system:
Aliphatic oxidation
Aromatic hydroxylation
N-Dealkylation
O-Dealkylation
S-Dealkylation
Epoxidation
Oxidative deamination
Sulfoxide formation
Desulfuration
N-Oxidation and N-hydroxylation
Dehalogenation

(2) Oxidation via non-microsomal mechanisms:
Alcohol and aldehyde oxidation
Purine oxidation
Oxidative deamination (monoamine oxidase and diamine oxidase)

(3) Reduction:

Azo and nitro reduction

(4) Hydrolysis:
Ester and amide hydrolysis
Peptide bond hydrolysis
Epoxide hydration

Phase II Reactions (conjugation reactions):

(1) Glucuronidation

(2) Acetylation

(3) Mercapturic acid formation

(4) Sulfate conjugation

(5) N-, O-, and S-methylation

(6) Trans-sulfuration

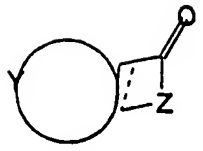
Typically, the compounds of formula I inhibitors used in the composition of the invention will have an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 100 uM or lower, preferably 25 uM or lower, more preferably 12 uM or lower and, even more preferably, 10 uM or lower.

Synthesis of Compounds

Many compounds inhibiting PARP activity can be synthesized by known methods from starting materials that are known, are themselves commercially available, or may be prepared by methods used to prepare corresponding compounds in the literature. See, for example, Suto et al., "Dihydroisoquinolinones: The Design and Synthesis of a New Series of Potent Inhibitors of Poly(ADP-Ribose) Polymerase", *Anticancer Drug Des.*, 7:107-17 (1991), which discloses processes for synthesizing a number of different PARP inhibitors.

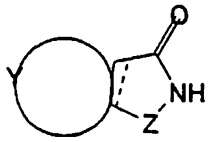
Preferred building blocks for synthesizing the compounds of formula I where X is double-bonded oxygen are phenanthridinones. As an example, the (5H)phenan-thridin-6-one compounds of the invention can be prepared by reacting a compound of formula IV:

IV

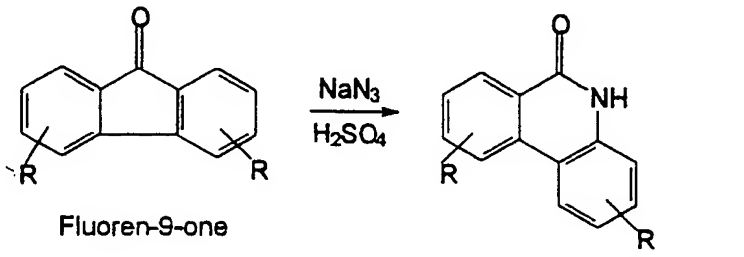


with a nitrogen-insertion agent, such as a combination of NaN_3 and H_2SO_4, to form a compound of formula V:

V



For example, the Schmidt method can be used in a conventional manner to make a (5H)phenanthridin-6-one from a fluorene-9-one as illustrated below:



In this example, the fluoren-9-one is generically substituted. Such fluoren-9-one starting derivatives are known in the chemistry literature and are accessible by processes known to one skilled in the art. Phenanthri-dinones can also be prepared through an intramolecular Heck reaction analogous to that disclosed by Chide et al., *Tetrahedron Lett.*, *32*:35, 4525-28 (1991).

Other methods that may be useful in preparing the compounds of the invention include, but are not limited to:

I. the Smith reaction of Respondly et al., *Acad. Sci. Paris, Ser. C*, (1967);

II. the photocyclization method described by Ninomiya et al.,

Tetrahedron Lett., 4451 (1970) and Ichiya et al., *J. Chem. Soc.*, *1*:2257 (1973);

III. isocyanate intramolecular cycloaddition reactions, such as that found in:

(a) Balazs et al., *Synthesis*, 1373 (1995)); Banwell et al., *J. Chem. Soc.*, *1*:3515 (1994);

(b) Migachev et al., *J. Org. Chem. USSR* (Eng. Trans.), *20*:8, 1565-71 (1984) and *Zh. Org. Khim.*, *20*:8, 1718-24 (1984);

(c) Migachev et al., *Chem. Heterocycl. Compd.* (Eng. Trans.), *17*:3, 289-94 (1981) and *Khim. Geterotsikl. Soedin.*, *17*:3, 388-91 (1981);

(d) Migatschew et al., *J. Gen. Chem. USSR* (Eng. Trans.); *48*, 2116, (1978));

(e) Chandler et al., *Aust. J. Chem.*, *20*, 2037-44 (1967));

(f) Ruediger et al., *Can. J. Chem*, *64*, 577-9 (1986).

The disclosures of the above-listed reference are hereby incorporated by reference. Other variations and modifications of the synthetic pathways described above will be obvious to those skilled in the art.

Pharmaceutical Compositions

A further aspect of the present invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or a diluent and a compound of formula I or a pharmaceutically acceptable salt, prodrug, metabolite, stereoisomer, or mixtures thereof (hereinafter, "compound of formula I"). Preferably, the compound of formula I is present in an amount effective for inhibiting PARP activity.

The formula I compounds of the invention are useful in the manufacture of pharmaceutical formulations comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. As such, formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, troche or lozenges, each containing a predetermined amount of the active

ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or nonaqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary, or paste.

The composition will usually be formulated into a unit dosage form such as a tablet, capsule, aqueous suspension or solution. Such formulations typically include a solid, semisolid, or liquid carrier. Exemplary carriers include lactose, cornstarch, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, mineral oil, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, methyl hydroxy-benzoate, propyl hydroxybenzoate, talc, magnesium stearate, and the like.

Preferred formulations are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dried cornstarch, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or glycine; and/or b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, and polyethylene glycol. Tablets may also contain binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl-cellulose, or polyvinyl-pyrrolidone. If desired, tablets may also contain disintegrants, e.g., starches, agar, alginic acid, or its sodium salt, or effervescent mixtures; and/or absorbents, colorants, flavors, and sweeteners. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient. The oral dosage forms may further contain sweetening and/or flavoring and/or coloring agents.

These compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, welling or emulsifying agents; solution promoters; salts for regulating the osmotic pressure, and/or buffers. In addition, they may also contain other therapeutically valuable substances. These compositions are prepared according to conventional mixing, granulating, or coating methods, respectively.

A tablet may be made by compressing or molding the active

ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

When administered parenterally, the composition will normally be in a unit dosage, sterile injectable form (aqueous isotonic solution, suspension or emulsion) with a pharmaceutically acceptable carrier. Such carriers are preferably non-toxic, parenterally-acceptable and contain non-therapeutic diluents or solvents. Examples of such carriers include water; aqueous solutions, such as saline (isotonic sodium chloride solution), Ringer's solution, dextrose solution, and Hanks' solution; and nonaqueous carriers, such as 1,3-butanediol, fixed oils (e.g., corn, cottonseed, peanut, sesame oil, and synthetic mono- or di-glyceride), ethyl oleate, and isopropyl myristate.

Oleaginous suspensions can be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. Among the acceptable solvents or suspending mediums are sterile fixed oils. For this purpose, any bland fixed oil may be used. Fatty acids, such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated forms, are also useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

Sterile saline is a preferred carrier, and the compounds are often sufficiently water soluble to be made up as a solution for all foreseeable needs. The carrier may contain minor amounts of additives, such as substances that enhance solubility, isotonicity, and chemical stability, e.g., anti-oxidants, buffers and preservatives.

When administered rectally, the composition will usually be formulated into a unit dosage form such as a suppository or cachet. These compositions can be prepared by mixing the

compound with suitable non-irritating excipients that are solid at room temperature, but liquid at rectal temperature, such that they will melt in the rectum to release the compound. Common excipients include cocoa butter, beeswax and polyethylene glycols or other fatty emulsions or suspensions.

Moreover, the compounds may be administered topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin or the lower intestinal tract.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH-adjusted sterile saline or, preferably, as a solution in isotonic, pH-adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, the compounds may be formulated into ointments, such as petrolatum.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene compound, polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application to the lower intestinal tract can be effected in rectal suppository formulations (see above) or in suitable enema formulations.

Formulations suitable for nasal or buccal administration, (such as self-propelling powder dispensing formulations), may comprise about 0.1% to about 5% w/w of the active ingredient or, for example, about 1% w/w of the same. In addition, some formulations can be compounded into a sublingual troche or lozenge.

The formulations may conveniently be presented in unit

dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

The composition of the invention is preferably administered as a capsule or tablet containing a single or divided dose of the inhibitor, or as a sterile solution, suspension, or emulsion, for parenteral administration in a single or divided dose.

In another preferred embodiment, the PARP inhibitor compounds of the invention can be prepared in lyophilized form. In this case, 1 to 100 mg of a PARP inhibitor may be lyophilized in individual vials, together with a carrier and a buffer, such as mannitol and sodium phosphate. The compound may be reconstituted in the vials with bacteriostatic water before administration.

In a preferred embodiment, the carrier is a solid biodegradable polymer or mixture of biodegradable polymers with appropriate time release characteristics and release kinetics. The composition of the invention may then be molded into a solid implant suitable for providing efficacious concentrations of the compounds of the invention over a prolonged period of time without the need for frequent redosing. The composition of the present invention can be incorporated into the biodegradable polymer or polymer mixture in any suitable manner known to one of ordinary skill in the art and may form a homogeneous matrix with the biodegradable polymer, or may be encapsulated in some way within the polymer, or may be molded into a solid implant.

In one embodiment, the biodegradable polymer or polymer mixture is used to form a soft "depot" containing the pharmaceutical composition of the present invention that can be administered as a flowable liquid, for example, by injection, but which remains sufficiently viscous to maintain the

pharmaceutical composition within the localized area around the injection site. The degradation time of the depot so formed can be varied from several days to a few years, depending upon the polymer selected and its molecular wight. By using a polymer composition in injectable form, even the need to make an incision may be eliminated. In any event, a flexible or flowable delivery "depot" will adjust to the shape of the space it occupies with the body with a minimum of trauma to surrounding tissues. The pharmaceutical composition of the present invention is used in amounts that are therapeutically effective and the amounts used may depend upon the desired release profile, the concentration of the pharmaceutical composition required for the sensitizing effect, and the length of time that the pharmaceutical composition has to be released for treatment.

The PARP inhibitors are used in the composition in amounts that are therapeutically effective. While the effective amount of the PARP inhibitor will depend on the particular inhibitor and the dosage form being used, amounts of the PARP inhibitor varying from about 0.1% to 75%, preferably about 1% to 65% and, even more preferably, about 1% to 50%, have been easily incorporated into liquid or solid carrier delivery systems.

Methods of Effecting Neuronal Activity

According to the methods of the invention, an effective therapeutic amount of the compounds and compositions described above are administered to animals to effect a neuronal activity, preferably one that is not mediated by NMDA neurotoxicity. Such neuronal activity may consist of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of a neurological disorder. Accordingly, the present invention further relates to a method of effecting a neuronal activity in an animal, comprising administering an effective amount of the compound of formula I to the animal. Further, the compounds of the invention inhibit PARP and, thus, are believed to be useful for treating neural tissue damage, particularly damage resulting from cerebral ischemia and reperfusion injury or neurodegenerative diseases in mammals.

The term "nervous tissue" refers to the various components that make up the nervous system including, without limitation, neurons, neural support cells, glia, Schwann cells, vasculature contained within and supplying these structures, the central nervous system, the brain, the brain stem, the spinal cord, the junction of the central nervous system with the peripheral nervous system, the peripheral nervous system, and allied structures.

The term "neural tissue damage resulting from ischemia and reperfusion injury and neurodegenerative diseases" includes neurotoxicity, such as seen in vascular stroke and global and focal ischemia.

The term "neurodegenerative diseases" includes Alzheimer's disease, Parkinson's disease and Huntington's disease.

The term "nervous insult" refers to any damage to nervous tissue and any disability or death resulting therefrom. The cause of nervous insult may be metabolic, toxic, neurotoxic, iatrogenic, thermal or chemical, and includes without limitation, ischemia, hypoxia, cerebrovascular accident, trauma, surgery, pressure, mass effect, hemorrhage, radiation, vasospasm, neuro-degenerative disease, infection, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, myelination/demyelination process, cognitive disorder, glutamate abnormality and secondary effects thereof.

The term "neuroprotective" refers to the effect of reducing, arresting or ameliorating nervous insult, and protecting, resuscitating or reviving nervous tissue which has suffered nervous insult.

The term "preventing neurodegeneration" includes the ability to prevent neurodegeneration in patients diagnosed as having a neurodegenerative disease or who are at risk of developing a neurodegenerative disease. The term also encompasses preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

Examples of neurological disorders that are treatable by the method of using the present invention include, without limitation, trigeminal neuralgia; glossopharyngeal neuralgia; Bell's Palsy; myasthenia gravis; muscular dystrophy;

amyotrophic lateral sclerosis; progressive muscular atrophy; progressive bulbar inherited muscular atrophy; herniated, ruptured or prolapsed invertebrate disk syndromes; cervical spondylosis; plexus disorders; thoracic outlet destruction syndromes; peripheral neuropathies such as those caused by lead, dapsone, ticks, porphyria, or Guillain-Barré syndrome; Alzheimer's disease; Huntington's disease and Parkinson's disease.

The method of the present invention is particularly useful for treating a neurological disorder selected from the group consisting of: peripheral neuropathy caused by physical injury or disease state, traumatic brain injury, physical damage to the spinal cord, stroke associated with brain damage, demyelinating diseases and neurological disorders related to neurodegeneration. Examples of demyelinating diseases include multiple sclerosis. Examples of neurological disorders relating to neurodegeneration include Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS).

The term "treating" refers to:

(i) preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and

(iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

Treating Other PARP-related Disorders

The compounds, compositions and methods of the present invention are particularly useful for treating or preventing tissue damage resulting from cell death or damage due to necrosis or apoptosis.

The compounds, compositions and methods of the invention can also be used to treat a cardiovascular disorder in an animal, by administering an effective amount of the compound of formula to the animal.

As used herein, the term "cardiovascular disorders" refers to those disorders that can either cause ischemia or are caused

by reperfusion of the heart. Examples include, but are not limited to, coronary artery disease, angina pectoris, myocardial infarction, cardiovascular tissue damage caused by cardiac arrest, cardiovascular tissue damage caused by cardiac bypass, cardiogenic shock, and related conditions that would be known by those of ordinary skill in the art or which involve dysfunction of or tissue damage to the heart or vasculature, especially, but not limited to, tissue damage related to PARP activation.

For example, the methods of the invention are believed to be useful for treating cardiac tissue damage, particularly damage resulting from cardiac ischemia or caused by reperfusion injury in animals. The methods of the invention are particularly useful for treating cardiovascular disorders selected from the group consisting of: coronary artery disease, such as atherosclerosis; angina pectoris; myocardial infarction; myocardial ischemia and cardiac arrest; cardiac bypass; and cardiogenic shock. The methods of the invention are particularly helpful in treating the acute forms of the above cardiovascular disorders.

Further, the methods of the invention can be used to treat tissue damage resulting from cell damage or death due to necrosis or apoptosis, neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; to prevent or treat vascular stroke; to treat or prevent cardiovascular disorders; to treat other conditions and/or disorders such as age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders (such as colitis and Crohn's disease), muscular dystrophy, osteoarthritis, osteoporosis, chronic and/or acute pain (such as neuropathic pain), renal failure, retinal ischemia, septic shock (such as endotoxic shock), and skin aging; to extend the lifespan and proliferative capacity of cells; to alter gene expression of senescent cells; or to radiosensitize tumor cells

Further still, the methods of the invention can be used to

treat cancer and to radiosensitize tumor cells. The term "cancer" is interpreted broadly. The compounds of the present invention can be "anti-cancer agents", which term also encompasses "anti-tumor cell growth agents" and "anti-neoplastic agents". For example, the methods of the invention are useful for treating cancers and radiosensitizing tumor cells in cancers such as ACTH-producing tumors, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head & neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovarian cancer, ovary (germ cell) cancer, prostate cancer, pancreatic cancer, penile cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, uterine cancer, vaginal cancer, cancer of the vulva and Wilm's tumor.

The term "radiosensitizer", as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to be radiosensitized to electromagnetic radiation and/or to promote the treatment of diseases which are treatable with electromagnetic radiation. Diseases which are treatable with electromagnetic radiation include neoplastic diseases, benign and malignant tumors, and cancerous cells. Electromagnetic radiation treatment of other diseases not listed herein are also contemplated by the present invention. The terms "electromagnetic radiation" and "radiation" as used herein includes, but is not limited to, radiation having the wavelength of 10^{-20} to 10^{0} meters. Preferred embodiments of the present invention employ the electromagnetic radiation of: gamma-radiation (10^{-20} to 10^{-13} m) x-ray radiation (10^{-11} to 10^{-9} m), ultraviolet light (10 nm to

400 nm), visible light (400 nm to 700 nm), infrared radiation (700 nm to 1.0 mm), and microwave radiation (1 mm to 30 cm).

Radiosensitizers are known to increase the sensitivity of cancerous cells to the toxic effects of electromagnetic radiation. Several mechanisms for the mode of action of radiosensitizers have been suggested in the literature including: hypoxic cell radiosensitizers (e.g., 2-nitroimidazole compounds, and benzotriazine dioxide compounds) promote the reoxygenation of hypoxic tissue and/or catalyze the generation of damaging oxygen radicals; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogs of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA molecules and/or prevent the normal DNA repair mechanisms; and various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

Many cancer treatment protocols currently employ radiosensitizers activated by the electromagnetic radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, NPe6, tin etioporphyrin SnET2, pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target

cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumor with or without additional radiation; or other therapeutically effective compounds for treating cancer or other disease. Examples of additional therapeutic agents that may be used in conjunction with radiosensitizers include, but are not limited to: 5-fluorouracil, leucovorin, 5'-amino-5'deoxythymidine, oxygen, carbogen, red cell transfusions, perfluorocarbons (e.g., Fluosol-DA), 2,3-DPG, BW12C, calcium channel blockers, pentoxyfylline, antiangiogenesis compounds, hydralazine, and L-BSO. Examples of chemotherapeutic agents that may be used in conjunction with radiosensitizers include, but are not limited to: adriamycin, camptothecin, carboplatin, cisplatin, daunorubicin, docetaxel, doxorubicin, interferon (alpha, beta, gamma), interleukin 2, irinotecan, paclitaxel, topotecan, and therapeutically effective analogs and derivatives of the same.

The compounds of the present invention may also be used for radiosensitizing tumor cells.

The term "treating" refers to:

(i) preventing a disease, disorder or condition from occurring in an animal that may be predisposed to the disease, disorder and/or condition, but has not yet been diagnosed as having it;

(ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and

(iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

Administration

In the methods of the present invention, the compounds may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, sublingually, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraosseous, intraperitoneal, intrathecal, intraventricular, intraspinal, intrasternal or intracranial injection and

infusion techniques and by subdural pump. Invasive techniques are preferred, particularly direct administration to damaged neuronal tissue.

To be effective therapeutically for central nervous system targets, the compounds used in the methods of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier, however, can still be effectively administered by an intraventricular route.

The compounds used in the methods of the present invention may be administered by a single dose, multiple discrete doses or continuous infusion. Since the compounds are small, easily diffusible and relatively stable, they are well suited to continuous infusion. Pump means, particularly subcutaneous pump means or as a subdural pump, are preferred for continuous infusion.

For medical use, the amount required of a compound of formula I to achieve a therapeutic affect will vary according to the particular compound administered, the route of administration, the mammal under treatment, and the particular disorder or disease concerned. It is understood that the ordinarily skilled physician or veterinarian will readily be able to determine and prescribe the amount of the compound effective for the desired prophylactic or therapeutic treatment. In so proceeding, the physician or veterinarian may employ an intravenous bolus followed by an intravenous infusion and repeated administrations, orally or parenterally, as considered appropriate. While it is possible for the compound of formula I to be administered alone, it is preferable to provide it as part of a pharmaceutical formulation.

Doses of the compounds preferably include pharmaceutical dosage units comprising an efficacious quantity of active compound. By an efficacious quantity is meant a quantity sufficient to inhibit PARP and derive the beneficial effects therefrom through administration of one or more of the pharmaceutical dosage units. Preferably, the dose is sufficient to prevent or reduce the effects of vascular stroke or other neurodegenerative diseases.

An exemplary daily dosage unit for a vertebrate host

comprises an amount of from about 0.001 mg/kg to about 50 mg/kg. Preferably, dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with even more preferred levels being about 0.1 mg to about 1,000 mg. More preferably, a suitable systemic dose of compound of formula I for a mammal suffering from, or likely to suffer from, any condition as described herein is in the range of about 0.1 to about 100 mg of the compound per kilogram of body weight, and most preferably, from about 1 to about 10 mg/kg of mammal body weight.

The specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; combination of the compound with other drugs; the severity of the particular disease being treated; the form of the drug; and the route of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

In methods of treating nervous insult (particularly acute ischemic stroke and global ischemia caused by drowning or head trauma), the compounds of the invention can be co-administered with one or more other therapeutic agents, preferably agents that can reduce the risk of stroke (such as aspirin) and, more preferably, agents that can reduce the risk of a second ischemic event (such as ticlopidine).

The compounds and compositions of the invention can be co-administered with one or more therapeutic agents either (i) together in a single formulation, or (ii) separately in individual formulations designed for optimal release rates of their respective active agent. Each formulation may contain from about 0.01% to about 99.99% by weight, preferably from about 3.5% to about 60% by weight, of the compound of the invention, as well as one or more pharmaceutical excipients, such as wetting, emulsifying and pH buffering agents. When the

compounds used in the methods of the present invention are administered in combination with one or more other therapeutic agents, specific dose levels for those agents will depend upon considerations such as those identified above for compounds, composition and methods of the invention in general.

TABLE VII below provides known median dosages for selected chemotherapeutic agents that may be administered in combination with the compounds of the invention to treat such diseases as various cancers.

TABLE VII

CHEMOTHERAPEUTIC AGENT	MEDIAN DOSAGE
Asparaginase	10,000 units
Bleomycin Sulfate	15 units
Carboplatin	50-450 mg
Carmustine	100 mg
Cisplatin	10-50 mg
Cladribine	10 mg
Cyclophosphamide (lyophilized)	100 mg to 2 gm
Cyclophosphamide (non-lyophilized)	100 mg to 2 gm
Cytarabine (lyophilized powder)	100 mg-2 gm
Dacarbazine	100-200 mg
Dactinomycin	0.5 mg
Daunorubicin	20 mg
Diethylstilbestrol	250 mg
Doxorubicin	10-150 mg
Etidronate	300 mg
Etoposide	100 mg
Floxuridine	500 mg
Fludarabine Phosphate	50 mg
Fluorouracil	500 mg to 5 gm
Goserelin	3.6 mg
Granisetron Hydrochloride	1 mg
Idarubicin	5-10 mg
Ifosfamide	1-3 gm
Leucovorin Calcium	50-350 mg

CHEMOTHERAPEUTIC AGENT	MEDIAN DOSAGE
Leuprolide	3.75-7.5 mg
Mechlorethamine	10 mg
Medroxyprogesterone	1 gm
Melphalan	50 gm
Methotrexate	20 mg to 1 gm
Mitomycin	5-40 mg
Mitoxantrone	20-30 mg
Ondansetron Hydrochloride	40 mg
Paclitaxel	30 mg
Pamidronate Disodium	30-90 mg
Pegaspargase	750 units
Plicamycin	2,500 mcgm
Streptozocin	1 gm
Thiotepa	15 mg
Teniposide	50 mg
Vinblastine	10 mg
Vincristine	1-5 mg
Aldesleukin	22 million units
Epoetin Alfa	2,000-10,000 units
Filgrastim	300-480 mcgm
Immune Globulin	500 mg to 10 gm
Interferon Alpha-2a	3-36 million units
Interferon Alpha-2b	3-50 million units
Levamisole	50 mg
Octreotide	1,000-5,000 mcgm
Sargramostim	250-500 mcgm

For the methods of the present invention, any administration regimen regulating the timing and sequence of delivery of the compound can be used and repeated as necessary to effect treatment. Such regimen may include pretreatment and/or co-administration with additional therapeutic agents.

To maximize protection of nervous tissue from nervous insult, the compounds of the invention should be administered

to the affected cells as soon as possible. In situations where nervous insult is anticipated, the compounds should be administered before the expected nervous insult. Such situations of increased likelihood of nervous insult include surgery (carotid endarterectomy, cardiac, vascular, aortic, orthopedic); endovascular procedures such as arterial catheterization (carotid, vertebral, aortic, cardia, renal, spinal, Adamkiewicz); injections of embolic agents; coils or balloons for hemostasis; interruptions of vascularity for treatment of brain lesions; and predisposing medical conditions such as crescendo transient ischemic attacks, emboli and sequential strokes.

Where pretreatment for stroke or ischemia is impossible or impracticable, it is important to get the compounds of the invention to the affected cells as soon as possible during or after the event. In the time period between strokes, diagnosis and treatment procedures should be minimized to save the cells from further damage and death.

A particularly advantageous mode of administration for a patient diagnosed with acute vascular stroke is by implantation as a subdural pump to deliver the compound(s) of the invention directly to the infarct area of the brain. Even if comatose, it is expected that the patient would recover more quickly that if he or she did not receive the compound. Further, it is expected that residual neurological symptoms and re-occurrence of vascular stroke would be reduced.

Depending on the patient's presenting symptoms and the response to the administration of the compound, the patient may receive the same or a different compound: parenterally, by injection or by intravenous administration; orally, by capsule or tablet; by implantation of a biocompatible, biodegradable polymeric matrix delivery system comprising the compound of formula I; or by direct administration to an infarct area by insertion of a subdural pump or a central line. It is expected that the treatment would alleviate the disorder, either in part or in its entirety and that no or fewer further occurrences of the disorder would develop. It also is expected that the patient would suffer fewer residual symptoms.

Examples of such disorders include, for example,

peripheral neuropathy caused by physical injury, peripheral neuropathy caused by disease state, Guillain-Barré syndrome, head trauma, physical damage to the spinal cord, vascular stroke associated with hypoxia and brain damage, focal cerebral ischemia, global cerebral ischemia, cerebral reperfusion injury, a demyelinating disease, multiple sclerosis, a neurological disorder relating to neurodegeneration, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), cardiovascular disease, such as acute coronary artery disease, acute cardiogenic shock, acute myocardial infarction, acute myocardial ischemia, full cardiac and respiratory arrest, septic shock, diabetes, arthritis, inflammatory bowel disorder such as colitis or Crohn's disease, and cancer.

Where the patient is diagnosed with an acute disorder prior to the availability of the compound of formula I, the patient's condition may deteriorate due to the disorder and become a chronic disorder by the time that the compounds of formula I are available. Even if the patient receives the compound after the disorder has become chronic, it is expected that the patient's condition would still improve and stabilize as a result of receiving the compound.

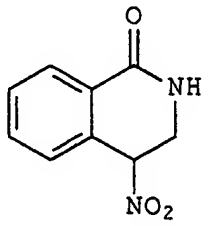
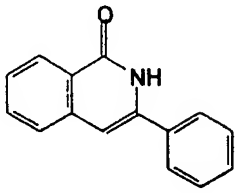
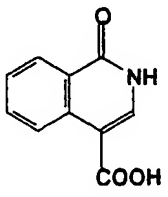
The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

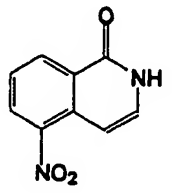
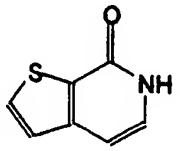
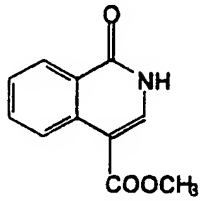
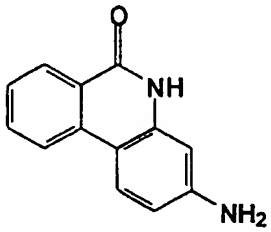
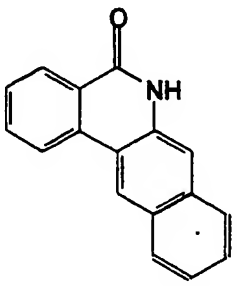
Example 1: Approximate IC_{50} Data for Selected PARP Inhibitors

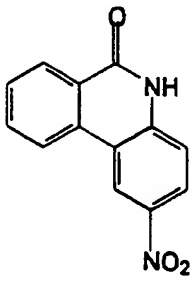
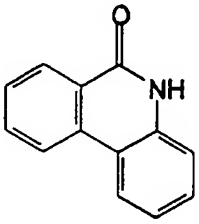
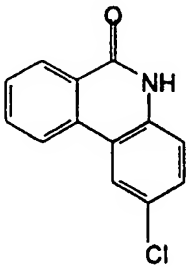
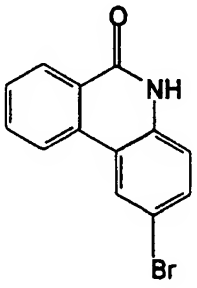
The IC_{50} of a PARP inhibitor compound is a PARP assay using purified recombinant human PARP from Trevigen (Gaithersburg, MD), as follows: The PARP enzyme assay was set up on ice in a volume of 100 microliters consisting of 10 mM Tris-HCl (pH 8.0), 1 mM $MgCl_2$, 28 mM KCl, 28 mM NaCl, 0.1 mg/ml of herring sperm DNA (activated as a 1 mg/ml stock for 10 minutes in a 0.15% hydrogen peroxide solution), 3.0 micromolar

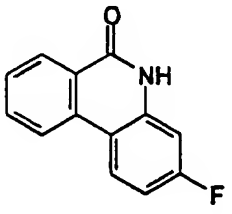
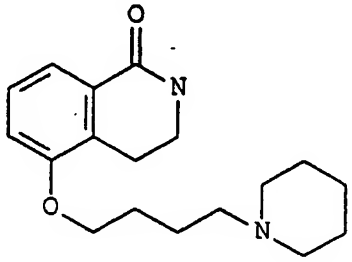
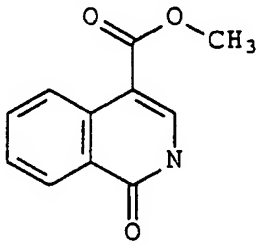
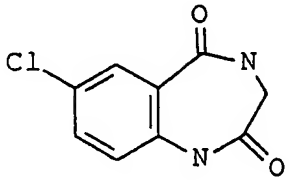
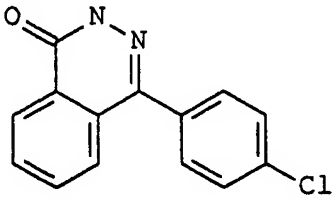
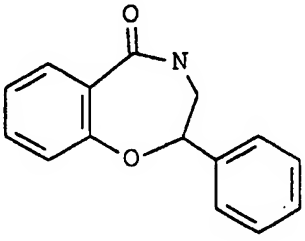
[3H]nicotinamide adenine dinucleotide (470 mci/mmole), 7 micrograms/ml PARP enzyme, and various concentrations of the compounds to be tested. The reaction was initiated by incubating the mixture at 25°C. After 15 minutes' incubation, the reaction was terminated by adding 500 microliters of ice cold 20% (w/v) trichloroacetic acid. The precipitate formed was transferred onto a glass fiber filter (Packard Unifilter-GF/B) and washed three times with ethanol. After the filter was dried, the radioactivity is determined by scintillation counting. The compounds of this invention were found to have potent enzymatic activity in the range of a tenths of μM to 20 M in IC_{50} in this inhibition assay. The IC_{50} data for the following compounds are shown below in TABLE VIII.

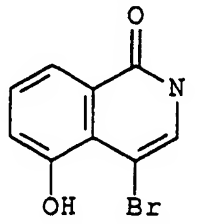
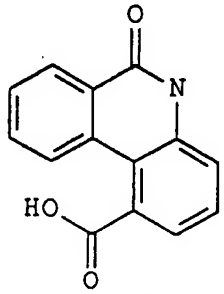
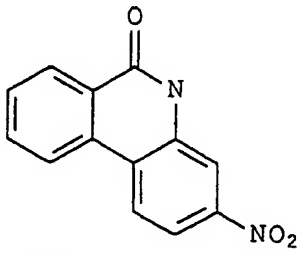
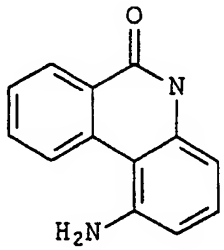
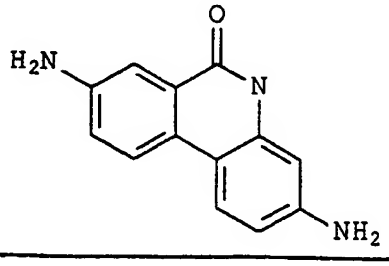
TABLE VIII

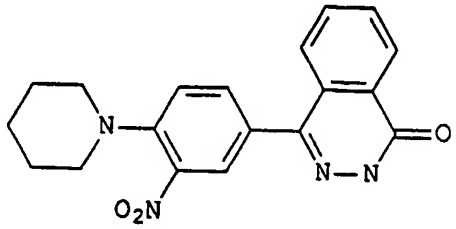
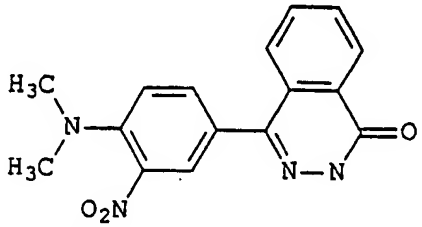
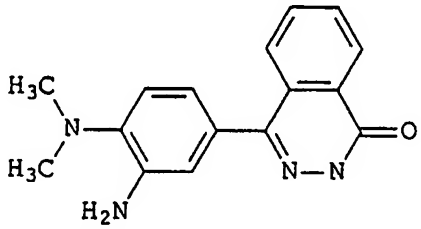
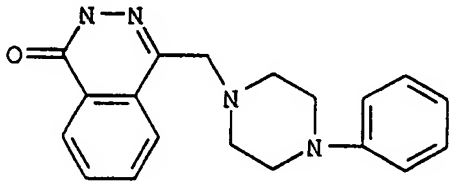
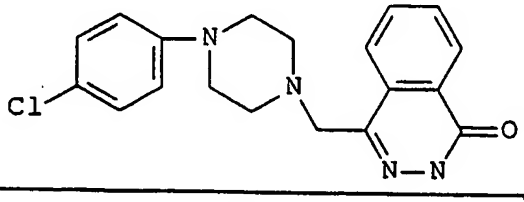
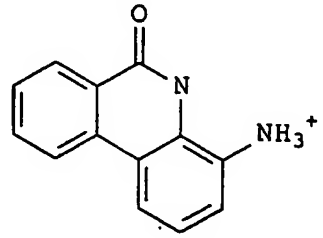
Compound	Approximate IC_{50}'s
	1.6 uM
	1.3 uM
	10 uM

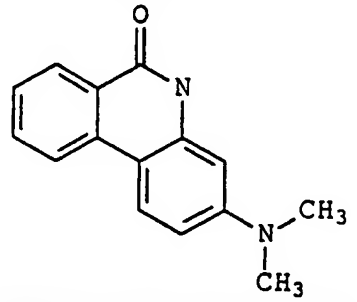
Compound	Approximate $IC_{50's}$
	3.4 uM
	50 uM
	0.8 uM
	4 μM
	100 μM

Compound	Approximate $IC_{50's}$
	0.9 μM
	5.2 μM
	0.7 μM
	1.1 μM

Compound	Approximate $IC_{50's}$
	0.2 μM
	1.9
	1.1
	1.6
	0.36
	1.9

Compound	Approximate IC_{50}'s
	0.60
	5.1
	0.16
	0.10
	3.26

Compound	Approximate $IC_{50's}$
	0.30
	0.68
	0.22
	4.0
	1.3
	0.76

Compound	Approximate $IC_{50's}$
	0.31

Example 2: Neuroprotective Effects on Focal Cerebral Ischemia in Rats:

Focal cerebral ischemia experiments are performed using male Wistar rats weighing about 250-300 g, which were anesthetized with 4% halothane. Anesthesia is maintained with 1.0-1.5% halothane until the end of surgery. The animals are installed in a warm environment to avoid a decrease in body temperature during surgery. An anterior midline cervical incision is made. The right common carotid artery (CCA) is exposed and isolated from the vagus nerve. A silk suture is placed and tied around the CCA in proximity to the heart. The external carotid artery (ECA) is then exposed and ligated with a silk suture. A puncture is made in the CCA, and a small catheter (PE 10, Ulrich & Co., St-Gallen, Switzerland) is gently advanced to the lumen of the internal carotid artery (ICA). The pterygopalatine artery is not occluded. The catheter is tied in place with a silk suture.

Then, a 4-0 nylon suture (Braun Medical, Crissier, Switzerland) is introduced into the catheter lumen and pushed until the tip blocks the anterior cerebral artery. The length of catheter into the ICA is approximately 19 mm from the origin of the ECA. The suture is maintained in this position by occlusion of the catheter with heat. One cm of catheter and nylon suture are left protruding so that the suture could be withdrawn to allow reperfusion. The skin incision is then closed with wound clips.

The animals are maintained in a warm environment during recovery from anesthesia. Two hours later, the animals are re-

anesthetized, the clips are discarded, and the wound is re-opened. The catheter is cut, and the suture is pulled out. The catheter is then obturated again with heat, and wound clips are placed on the wound. The animals are allowed to survive for 24 hours with free access to food and water. The rats are then sacrificed with CO_2 and decapitated.

The brains are immediately removed, frozen on dry ice and stored at -80°C. The brains are then cut in 0.02 mm-thick sections in a cryocut at -19°C, selecting one of every 20 sections for further examination. The sections are stained with cresyl violet according to the Nissl procedure. Each stained section is examined under a light microscope, and the regional infarct area is determined according to the presence of cells with morphological changes.

Various doses of compounds of the invention are tested in this model. The compounds are given either intravenously or intraperitoneally, as a single dose or as a series of multiple doses, and are given at different times, both before or after the onset of ischemia. It is expected by the inventors that the compounds of the invention would provide protection from ischemia in the range of about 20 to 80 per cent.

Example 3: Neuroprotective Effects on Focal Cerebral Ischemia in Rats:

Female Sprague-Dawley rats, each weighing about 300-350 g, are anesthetized with intraperitoneal ketamine at a dose of 150 mg/kg. The rats are endotracheally intubated and ventilated with oxygen-enriched room air using a Harvard rodent ventilator. Polyethylene catheters inserted into the carotid artery and into the femoral vein are used for monitoring artery blood pressure and fluid administration respectively. Arterial pCO_2 is maintained between about 35 and 45 mm Hg by adjusting the respirator rate.

The rat chests are opened by median sternotomy, the pericardium is incised, and the hearts are cradled with a latex membrane tent. Hemodynamic data are obtained at baseline after at least a 15-minute stabilization period following the end of the surgical operation. The LAD (left anterior descending) coronary artery is ligated for 40 minutes, and then re-perfused

for 120 minutes. After the 120-minute reperfusion, the LAD artery is re-occluded, and a 0.1 ml bolus of monastral blue dye is injected into the left atrium to determine the ischemic risk region.

The hearts are then arrested with potassium chloride and cut into five 2-3 mm thick transverse slices. Each slice is weighed and incubated in a 1% solution of triphenyltetrazolium chloride to visualize the infarcted myocardium located within the risk region. Infarct size is calculated by summing the values for each left ventricular slice and is further expressed as a fraction of the risk region of the left ventricle.

Various doses of the compounds of the invention are tested in this model. The compounds are given either intravenously or intraperitoneally, in a single dose or as a series of multiple doses, and are given at different times, both before or after the onset of ischemia. It is expected by the inventors that the compounds of the invention would provide protection against ischemia/ reperfusion injury in the range of about 10 to 40 per cent.

Example 4: Neuroprotective Effects on Focal Cerebral Ischemia in Rats:

Focal cerebral ischemia was produced by cauterization of the right distal MCA (middle cerebral artery) with bilateral temporary common carotid artery occlusion in male Long-Evans rats for 90 minutes. All procedures performed on the animals were approved by the University Institutional Animal Care and Use Committee of the University of Pennsylvania. A total of 42 rats (weights: 230-340 g) obtained from Charles River were used in this study. The animals fasted overnight with free access to water prior to the surgical procedure.

Two hours prior to MCA occlusion, varying amounts (control, n=14; 5 mg/kg, n=7; 10 mg/kg, n=7; 20 mg/kg, n=7; and 40 mg/kg, n=7) of the PARP inhibitor compound, 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone ("DPQ"), were dissolved in dimethyl sulfoxide (DMSO) using a sonicator. A volume of 1.28 ml/Kg of the resulting solution was injected intraperitoneally into fourteen rats.

The rats were then anesthetized with halothane (4% for

induction and 0.8%-1.2% for the surgical procedure) in a mixture of 70% nitrous oxide and 30% oxygen. The body temperature was monitored by a rectal probe and maintained at 37.5 ± 0.5°C with a heating blanket regulated by a homeothermic blanket control unit (Harvard Apparatus Limited, Kent, U.K.). A catheter (PE-50) was placed into the tail artery, and arterial pressure was continuously monitored and recorded on a Grass polygraph recorder (Model 7D, Grass Instruments, Quincy, Massachusetts). Samples for blood gas analysis (arterial pH, PaO_2 and $PaCO_2$) were also taken from the tail artery catheter and measured with a blood gas analyzer (ABL 30, Radiometer, Copenhagen, Denmark). Arterial blood samples were obtained 30 minutes after MCA occlusion.

The head of the animal was positioned in a stereotaxic frame, and a right parietal incision between the right lateral canthus and the external auditory meatus was made. Using a dental drill constantly cooled with saline, a 3 mm burr hole was prepared over the cortex supplied by the right MCA, 4 mm lateral to the sagittal suture and 5 mm caudal to the coronal suture. The dura mater and a thin inner bone layer were kept, care being taken to position the probe over a tissue area devoid of large blood vessels. The flow probe (tip diameter of 1 mm, fiber separation of 0.25 mm) was lowered to the bottom of the cranial burr hole using a micromanipulator. The probe was held stationary by a probe holder secured to the skull with dental cement. The microvascular blood flow in the right parietal cortex was continuously monitored with a laser Doppler flowmeter (FloLab, Moor, Devon, U.K., and Periflux 4001, Perimed, Stockholm, Sweden).

Focal cerebral ischemia was produced by cauterization of the distal portion of the right MCA with bilateral temporary common carotid artery (CCA) occlusion by the procedure of Chen et al., "A Model of Focal Ischemic Stroke in the Rat: Reproducible Extensive Cortical Infarction", *Stroke*, *17*:738-43 (1986) and/or Liu et al., "Polyethylene Glycol-conjugated Superoxide Dismutase and Catalase Reduce Ischemic Brain Injury", *Am. J. Physiol.*, *256*:H589-93 (1989), both of which are hereby incorporated by reference.

Specifically, bilateral CCA's were isolated, and loops made from polyethylene (PE-10) catheter were carefully passed around the CCA's for later remote occlusion. The incision made previously for placement of the laser doppler probe was extended to allow observation of the rostral end of the zygomatic arch at the fusion point using a dental drill, and the dura mater overlying the MCA was cut. The MCA distal to its crossing with the inferior cerebral vein was lifted by a fine stainless steel hook attached to a micromanipulator and, following bilateral CCA occlusion, the MCA was cauterized with an electrocoagulator. The burr hole was covered with a small piece of Gelform, and the wound was sutured to maintain the brain temperature within the normal or near-normal range.

After 90 minutes of occlusion, the carotid loops were released, the tail arterial catheter was removed, and all of the wounds were sutured. Gentamicin sulfate (10 mg/ml) was topically applied to the wounds to prevent infection. The anesthetic was discontinued, and the animal was returned to his cage after awakening. Water and food were allowed ad libitum.

Two hours after MCA occlusion, the animals were given the same doses of the PARP inhibitor as in the pre-treatment. Twenty-four hours after MCA occlusion, the rats were sacrificed with an intraperitoneal injection of pentobarbital sodium (150 mg/kg). The brain was carefully removed from the skull and cooled in ice-cold artificial CSF for five minutes. The cooled brain was then sectioned in the coronal plane at 2 mm intervals using a rodent brain matrix (RBM-4000C, ASI Instruments, Warren, Michigan). The brain slices were incubated in phosphate-buffered saline containing 2% 2,3,5-triphenyl-tetrazolium chloride (TTC) at 37°C for ten minutes. Color photographs were taken of the posterior surface of the stained slices and were used to determine the damaged area at each cross-sectional level using a computer-based image analyzer (NIH Image 1.59). To avoid artifacts due to edema, the damaged area was calculated by subtracting the area of the normal tissue in the hemisphere ipsilateral to the stroke from the area of the hemisphere contralateral to the stroke, by the method of Swanson et al., "A Semiautomated Method for Measuring Brain Infarct Volume", *J. Cereb. Blood Flow Metabol.*, *10*:290-93

(1990), the disclosure of which is hereby incorporated by reference. The total volume of infarction was calculated by summation of the damaged volume of the brain slices.

The cauterization of the distal portion of the right MCA with bilateral temporary CCA occlusion consistently produced a well-recognized cortical infarct in the right MCA territory of each test animal. There was an apparent uniformity in the distribution of the damaged area as measured by TTC staining in each group, as shown in Figure 1.

In Figure 1, the distribution of the cross-sectional infarct area at representative levels along the rostrocaudal axis was measured from the interaural line in non-treated animals and in animals treated with 10 mg/kg of 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone. The area of damage was expressed as mean ± standard deviation. Significant differences between the 10 mg-treated group and the control group were indicated ($^{*}p<0.02$, $^{**}p<0.01$, $^{**}p<0.001$). The 5 mg/kg and 20 mg/kg curves fell approximately halfway between the control and the 10 mg/kg curves, whereas the 40 mg/kg curve was close to the control. The 5, 20 and 40 mg/kg curves were omitted for clarity.

PARP inhibition led to a significant decrease in the damaged volume in the 5 mg/kg-treated group (106.7 ± 23.2 mm^3, $p<0.001$), the 10 mg/kg-treated group (76.4 ± 16.8 mm^3, $p<0.001$), and the 20 mg/kg-treated group (110.2 ± 42.0 mm^3, $p<0.01$), compared to the control group (165.2 ± 34.0 mm^3. The data are expressed as mean ± standard deviation. The significance of differences between groups was determined using an analysis of variance (ANOVA) followed by Student's t-test for individual comparisons.

There was no significant difference between the control and the 40 mg/kg-treated group (135.6 ± 44.8 mm^3). However, there were significant differences between the 5 mg/kg-treated group and the 10 mg/kg-treated group ($p<0.02$), and between the 10 mg/kg-treated group and the 40 mg/kg-treated group ($p<0.01$), as shown in Figure 2.

In Figure 2, the effect of intraperitoneal administration of 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone on the infarct volume was depicted graphically.

The volumes of infarct were expressed as mean ± standard deviation. Significant differences between the treated groups and the control group were indicated ($^{*}p<0.01$, $^{**}p<0.001$). It is not clear why a high dose (40 mg/kg) of the PARP inhibitor, 3,4-dihydro-5-[4-(1-piperidinyl)-butoxy]-1(2H)-isoquinolinone, was less neuroprotective. The U-shaped dose-response curve may suggest dual effects of the compound.

However, overall, the in vivo administration of the inhibitor led to a substantial reduction in infarct volume in the focal cerebral ischemia model in the rat. This result indicated that the activation of PARP plays an important role in the pathogenesis of brain damage in cerebral ischemia.

The values of arterial blood gases (PaO_2, $PaCO_2$ and pH) were within the physiological range in the control and treated groups with no significant differences in these parameters among the five groups, as shown below in Table IX. A "steady state" MABP was taken following completion of the surgical preparation, just prior to occlusion; an "ischemia" MABP was taken as the average MABP during occlusion.

TABLE IX

	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pH	MABP (mm Hg) Steady State	MABP (mm Hg) Ischemia
Control group (n=4)	125±21	38.6 ± 4.6	7.33 ± 0.05	79±14	91±13**
5 mg/kg-treated group (n=7)	126±20	38.0 ± 2.8	7.36 ± 0.02	78± 5	91±12**
10 mg/kg-treated group (n=7)	125±16	39.3 ± 5.2	7.34 ± 0.03	80± 9	90±14*
20 mg/kg-treated group (n=7)	122±14	41.3 ± 2.8	7.35 ± 0.23	79±10	91±12**
40 mg/kg-treated group (n=7)	137±17	39.5 ± 4.7	7.33 ± 0.24	78± 4	88±12*

* = Significantly different from the steady state value, $p<0.05$.

** = Significantly different from the steady state value, $p<0.01$.

There were no significant differences in any physiological

parameter, including mean arterial blood pressure (MABP), prior to MCA and CCA occlusion among the five groups. Although MABP was significantly elevated following occlusion in all five groups, there were no significant differences in MABP during the occlusion period among the groups.

Since the blood flow values obtained from the laser doppler were in arbitrary units, only percent changes from the baseline (prior to occlusion) were reported. Right MCA and bilateral CCA occlusion produced a significant decrease in relative blood flow in the right parietal cortex to 20.8 $\pm$ 7.7 % of the baseline in the control group (n=5), 18.7 $\pm$ 7.4 % in the 5 mg/kg-treated group (n=7), 21.4 $\pm$ 7.7 % in the 10 mg/kg-treated group (n=7) and 19.3 $\pm$ 11.2 % in the 40 mg/kg-treated group (n=7). There were no significant differences in the blood flow response to occlusion among the four groups. In addition, blood flow showed no significant changes throughout the entire occlusion period in any group.

Following release of the carotid occlusions, a good recovery of blood flow (sometimes hyperemia) was observed in the right MCA territory of all animals. Reperfusion of the ischemic tissue resulted in the formation of NO and peroxynitrite, in addition to oxygen-derived free radicals. All of these radicals have been shown to cause DNA strand breaks and to activate PARP.

Example 5: Retinal Ischemia Protection

A patient just diagnosed with acute retinal ischemia is immediately administered parenterally, either by intermittent or continuous intravenous administration, a compound of formula I, either as a single dose or a series of divided doses of the compound. After this initial treatment, and depending on the patient's presenting neurological symptoms, the patient optionally may receive the same or a different compound of the invention in the form of another parenteral dose. It is expected by the inventors that significant prevention of neural tissue damage would ensue and that the patient's neurological symptoms would considerably lessen due to the administration of the compound, leaving fewer residual neurological effects post-stroke. In addition, it is expected that the re-occurrence of

retinal ischemia would be prevented or reduced.

Example 6: Treatment of Retinal Ischemia

A patient has just been diagnosed with acute retinal ischemia. Immediately, a physician or a nurse parenterally administers a compound of formula I, either as a single dose or as a series of divided doses. The patient also receives the same or a different PARP inhibitor by intermittent or continuous administration via implantation of a biocompatible, biodegradable polymeric matrix delivery system comprising a compound of formula I, or via a subdural pump inserted to administer the compound directly to the infarct area of the brain. It is expected by the inventors that the patient would awaken from the coma more quickly than if the compound of the invention were not administered. The treatment is also expected to reduce the severity of the patient's residual neurological symptoms. In addition, it is expected that re-occurrence of retinal ischemia would be reduced.

Example 7 Vascular Stroke Protection

A patient has just been diagnosed with acute vascular stroke and is immediately administered a compound of formula I, either as a single dose or as a series of divided doses of the compound. After this initial treatment and, depending upon the patient's neurological symptoms, the patient may receive another dose of the same or a different compound of the invention in parenteral form, such as by intermittent or continuous intravenous infusion, or in the form of a capsule or tablet. It is expected by the inventors that further neural tissue damage would be prevented to a significant degree, that the patient's neurological symptoms would considerably lessen, and that there would be fewer residual neurological effects post-stroke. In addition, it is expected by the inventors that the re-occurrence of vascular stroke would be reduced or prevented.

Example 8: Treatment of Vascular Stroke

A patient has just been diagnosed with acute multiple vascular strokes and is comatose. Immediately, a physician or

a nurse parenterally administers a single dose or a series of divided doses of a compound of formula I. Due to the comatose state of the patient, the patient will receive the same or a different compound by intermittent or continuous administration via implantation of a biocompatible, biodegradable polymeric matrix delivery system comprising the compound. A subdural pump could also be inserted to provide for administration of the compound directly to the infarct area of the brain. It is expected by the inventors that the patient would awaken from the coma more quickly than if the compound of the invention had not been administered. The treatment is also expected to reduce the severity of the patient's residual neurological symptoms. In addition, the inventors expect that re-occurrence of vascular stroke would be reduced for this patient.

Example 9: Preventing Cardiac Reperfusion Injury

A patient is diagnosed with life-threatening cardiomyopathy and requires a heart transplant. Until a donor heart is found, the patient is maintained on Extra Corporeal Oxygenation Monitoring (ECMO). A donor heart is located, and the patient undergoes a transplant procedure in which the patient is placed on a heart-lung pump during the surgical procedure. The patient receives a pharmaceutical composition containing a compound of formula I intracardiac within a specified period of time prior to the re-routing of the patient's circulation from the heart-lung pump to his or her own new heart, thus preventing cardiac reperfusion injury when the patient's new heart starts pumping to circulate the patient's blood.

Example 10: Septic Shock Assay

Groups of 10 C57/BL male mice weighing 18 to 20 g are administered a test compound of Formula I at the doses of 60, 20, 6 and 2 mg/kg, daily, by intraperitoneal (IP) injection for three consecutive days. Each animal is first challenged with lipopolysaccharide (LPS, from E. Coli, LD_{100} of 20 mg/animal IV) plus galactosamine (20 mg/animal IV). The first dose of test compound in a suitable vehicle is given 30 minutes after challenge, and the second and third doses are given 24 hours

later on day 2 and day 3 respectively, with only the surviving animals receiving the second or third dose of the test compound. Mortality was recorded every 12 hours after challenge for the three-day testing period. Compounds of Formula I provide protection against mortality from septic shock of about 40%. Based on these results, other compounds of the invention are expected to provide a protection against mortality exceeding about 35%.

Example 11: *In vitro* Radiosensitization

The human prostate cancer cell line, PC-3s, are plated in 6 well dishes and grown at monolayer cultures in RPMI1640 supplemented with 10% FCS. The cells are maintained at 37°C in 5% CO_2 and 95% air. The cells are exposed to a dose response (0.1 mM to 0.1 uM) of 3 different PARP inhibitors of Formula I disclosed herein prior to irradiation at one sublethal dose level. For all treatment groups, the six well plates are exposed at room temperature in a Seifert 250kV/15mA irradiator with a 0.5 mm Cu/1 mm. Cell viability is examined by exclusion of 0.4% trypan blue. Dye exclusion is assessed visually by microscopy and viable cell number is calculated by subtracting the number of cells from the viable cell number and dividing by the total number of cells. Cell proliferation rates are calculated by the amount of ^{3}H-thymidine incorporation post-irradiation. The PARP inhibitors show radiosensitization of the cells.

Example 12 *In vivo* Radiosensitization

Before undergoing radiation therapy to treat cancer, a patient is administered an effective amount of a compound or a pharmaceutical composition of the present invention. The compound or pharmaceutical composition acts as a radiosensitizer and making the tumor more susceptible to radiation therapy.

Example 13 Measuring Altered Gene Expression in mRNA Senescent Cells

Human fibroblast BJ cells, at Population Doubling (PDL) 94, are plated in regular growth medium and then changed to low

serum medium to reflect physiological conditions described in Linskens, et al., *Nucleic Acids Res.* 23:16:3244-3251 (1995). A medium of DMEM/199 supplemented with 0.5% bovine calf serum is used. The cells are treated daily for 13 days with the PARP inhibitor of Formula I as disclosed herein. The control cells are treated with and without the solvent used to administer the PARP inhibitor. The untreated old and young control cells are tested for comparison. RNA is prepared from the treated and control cells according to the techniques described in PCT Publication No. 96/13610 and Northern blotting is conducted. Probes specific for senescence-related genes are analyzed, and treated and control cells compared. In analyzing the results, the lowest level of gene expression is arbitrarily set at 1 to provide a basis for comparison. Three genes particularly relevant to age-related changes in the skin are collagen, collagenase and elastin. West, *Arch. Derm.* 130:87-95 (1994). Elastin expression of the cells treated with the PARP inhibitor of Formula I is significantly increased in comparison with the control cells. Elastin expression is significantly higher in young cells compared to senescent cells, and thus treatment with the PARP inhibitor of Formula I causes elastin expression levels in senescent cells to change to levels similar to those found in much younger cells. Similarly, a beneficial effect is seen in collagenase and collagen expression with treatment with the PARP inhibitors of Formula I.

Example 14 Measuring Altered Gene Expression Protein in Senescent Cells

Approximately 105 BJ cells, at PDL 95-100 are plated and grown in 15 cm dishes. The growth medium is DMEM/199 supplemented with 10% bovice calf serum. The cells are treated daily for 24 hours with the PARP inhibitors of Formula I (100 ug/ 1 mL of medium). The cells are washed with phosphate buffered solution (PBS), then permeablized with 4% paraformaldehyde for 5 minutes, then washed with PBS, and treated with 100% cold methanol for 10 minutes. The methanol is removed and the cells are washed with PBS, and then treated with 10% serum to block nonspecific antibody binding. About 1 mL of the appropriate commercially available antibody solutions

(1:500 dilution). Vector is added to the cells and the mixture incubated for 1 hour. The cells are rinsed and washed three times with PBS. A secondary antibody, goat anti-mouse IgG (1 mL) with a biotin tag is added along with 1 mL of a solution containing streptavidin conjugated to alkaline phosphatase and 1 mL of NBT reagent (Vector). The cells are washed and changes in gene expression are noted colorimetrically. Four senescence-specific genes -- collagen I, collagen III, collagenase, and interferon gamma -- in senescent cells treated with the PARP inhibitor of Formula I are monitored and the results show a decrease in interferon gamma expression with no observable change in the expression levels of the other three genes, demonstrating that the PARP inhibitors of Formula I can alter senescence-specific gene expression.

Example 15 Extending or Increasing Proliferative Capacity and Lifespan of Cells

To demonstrate the effectiveness of the present method for extending the proliferative capacity and lifespan of cells, human fibroblast cells lines (either W138 at Population Doubling (PDL) 23 or BJ cells at PDL 71) are thawed and plated on T75 flasks and allowed to grow in normal medium (DMEM/M199 plus 10% bovine calf serum) for about a week, at which time the cells are confluent, and the cultures are therefor ready to be subdivided. At the time of subdivision, the media is aspirated, and the cells rinsed with phosphate buffer saline (PBS) and then trypsinized. The cells are counted with a Coulter counter and plated at a density of 10^5 cells per cm^2 in 6-well tissue culture plates in DMEM/199 medium supplemented with 10% bovine calf serum and varying amounts (0.10uM, and 1mM: from a 100X stock solution in DMEM/M199 medium) of a PARP inhibitor of Formula I as disclosed herein. This process is repeated every 7 days until the cell appear to stop dividing. The untreated (control) cells reach senescence and stop dividing after about 40 days in culture. Treatment of cells with 10 uM 3-AB appears to have little or no effect in contrast to treatment with 100 uM 3-AB which appears lengthen the lifespan of the cells and treatment with 1 mM 3-AB which dramatically increases the lifespan and proliferative capacity

of the cells. The cells treated with 1 mM 3-AB will still divide after 60 days in culture.

Example 16: Neuroprotective Effects of Formula I on Chronic Constriction Injury (CCI) in Rats

Adult male Sprague-Dawley rats, 300-350 g, are anesthetized with intraperitoneal 50 mg/kg sodium pentobarbital. Nerve ligation is performed by exposing one side of the rat's sciatic nerves and dissecting a 5-7 mm-long nerve segment and closing with four loose ligatures at a 1.0-1.5-mm, followed by implanting of an intrathecal catheter and inserting of a gentamicin sulfate-flushed polyethylene (PE-10) tube into the subarachnoid space through an incision at the cisterna magna. The caudal end of the catheter is gently threaded to the lumbar enlargement and the rostral end is secured with dental cement to a screw embedded in the skull and the skin wound is closed with wound clips.

Thermal hyperalgesia to radiant heat is assessed by using a paw-withdrawal test. The rat is placed in a plastic cylinder on a 3-mm thick glass plate with a radiant heat source from a projection bulb placed directly under the plantar surface of the rat's hindpaw. The paw-withdrawal latency is defined as the time elapsed from the onset of radiant heat stimulation to withdrawal of the rat's hindpaw.

Mechanical hyperalgesia is assessed by placing the rat in a cage with a bottom made of perforated metal sheet with many small square holes. Duration of paw-withdrawal is recorded after pricking the mid-plantar surface of the rat's hindpaw with the tip of a safety pin inserted through the cage bottom.

Mechano-allodynia is assessed by placing a rat in a cage similar to the previous test, and applying von Frey filaments in ascending order of bending force ranging from 0.07 to 76 g to the mid-plantar surface of the rat's hindpaw. A von Frey filament is applied perpendicular to the skin and depressed slowly until it bends. A threshold force of response is defined as the first filament in the series to evoke at least one clear paw-withdrawal out of five applications.

Dark neurons are observed bilaterally within the spinal cord dorsal horn, particularly in laminae I-II, of rats 8 days

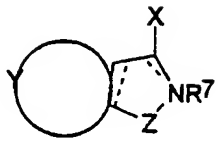
after unilateral sciatic nerve ligation as compared with sham operated rats. Various doses of differing compounds of Formula I are tested in this model and show that the Formula I compounds reduce both incidence of dark neurons and neuropathic pain behavior in CCI rats.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications are intended to be included within the scope of the following claims.

We claim:

1. A compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, -

NO_2, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

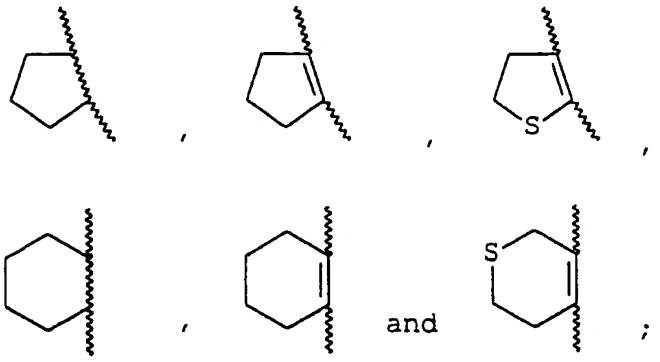
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

with the provisos that:

(a) when X is double-bonded oxygen, and Z is $-CHR^2CHR^3-$, R^3 cannot be hydrogen or methyl;

(b) when X is double-bonded oxygen, and Z is $-R^6C=CR^3-$, R^3 cannot be methyl, phenyl, or $-(CH_2)_4-C\equiv CH$;

(c) when R^3 and R^6 are taken together to form a fused aromatic ring, Y cannot be a ring selected from the group consisting of:



(d) when X, Y and Z, taken together, form a phenanthridone, a phenanthridinone, a phenanthrene, or a phenanthridine nucleus with an amino group or an aminoalkoxylene group in the 3-position, the 8-position cannot also be substituted with an amino group or an aminoalkoxylene group; and

(e) when X is a double bonded oxygen, and Z is a 6-membered unsaturated ring, and Y is phenyl, then the 2-position of the Z-ring cannot be substituted

with a hydrogen or a nitro group;

(f) when X is -OH or double bonded oxygen and Z is -CH=CH-, then Y is not phenyl or 5-hydroxyphenyl;

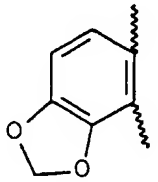
(g) when X is a double bonded oxygen, and Z is -CH=N-, then Y is not phenyl;

(h) when X is a double bonded oxygen, and Z is -C(O)NH-, then Y is not aminophenyl.

2. The compound of claim 1, wherein X is double-bonded oxygen.

3. The compound of claim 1, wherein Y has at least one site of unsaturation.

4. The compound of claim 1, wherein Y represents the atoms necessary to form a fused phenyl, naphthalene ring, or



5. The compound of claim 1, wherein Y is substituted with at least one non-hydrogen, non-interfering substituent.

6. The compound of claim 5, wherein said substituent is selected from the group consisting of $-NO_2$, halo, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, aralkyl, $-COOR^1$, $-OR^1$ or $-NHR^1$, where R^1 is hydrogen, lower alkyl, or aralkyl.

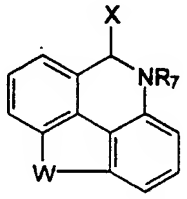
7. The compound of claim 1, wherein Z is (i) $-CHR^2CHR^3-$, (ii) $-R^6C=CR^3-$, or (iii) $-R^2C=N-$.

8. The compound of claim 1, wherein Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused aromatic ring.

9. The compound of claim 8, wherein said ring is substituted with at least one non-hydrogen substituent

selected from the group consisting of halo, amino, nitro, hydroxy, piperidine, piperazine, imidazolidine, dimethylamino, aryl, and arylalkyl.

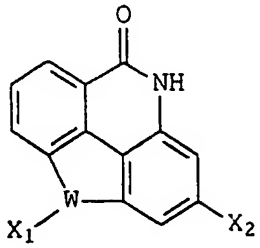
10. The compound of claim 1, wherein said compound has an isoquinoline, a pteridine, a phenanthridine, a phthalazine, or a quinazoline nucleus, or a tetracyclic bridging structure to ring Y, having the formula:



where W is -O-, -S-, -NR^1-, -CHO, -CHOH, or -$CHNH_2$ where R^1 is hydrogen or lower alkyl.

11. The compound of claim 10, wherein said compound has a phenanthridine nucleus.

12. The compound of claim 1, wherein said compound has a tetracyclic bridging structure to ring Y, having the formula:



where W is -CH-; X_1 is hydrogen, hydroxy, or amino; and X_2 is hydrogen, amino, 1-piperidine, 1-piperazine, 1-imidazolidine, or hydroxy.

13. The compound of claim 1, wherein R^7, when present, is hydrogen.

14. The compound of claim 1, wherein said compound has

an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 25 uM or lower.

15. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a chloro group.

16. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a bromo group.

17. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring substituted with a $-NO_2$ group; and
Z is $-R^6C=CR^3-$ where, R^6 and R^3, taken together, form a fused benzene ring substituted with an amino group.

18. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring with a bridging substituent connecting the Z ring with the Y ring.

19. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with an $-NO_2$ group.

20. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying at least one non-hydrogen, non-interfering substituent; and

Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form an unsubstituted fused benzene ring.

21. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying a chloro substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with a chloro group.

22. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^5, taken together, form a fused benzene ring substituted with a -Br and a $-NO_2$ group.

23. The compound of claim 1, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R_6C=CR^3-$ where R^6 and R^3, taken together, form a fused naphthalene ring.

24. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-10-methylphenanthridin-6-one.

25. The compound of claim 1, wherein said compound is 5(*H*)2-nitro-10-methylphenanthridin-6-one.

26. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-10-aminophenanthridin-6-one.

27. The compound of claim 1, wherein said compound is 5(*H*)2-nitro-10-aminophenanthridin-6-one.

28. The compound of claim 1, wherein said compound is 5(*H*) 2-chloro-10-nitrophenanthridin-6-one.

29. The compound of claim 1, wherein said compound is 5(*H*)2,10-dinitrophenanthridin-6-one.

30. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-10-hydroxyphenanthridin-6-one.

31. The compound of claim 1, wherein said compound is 5(*H*)2-nitro-10-hydroxyphenanthridin-6-one.

32. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-10-bromophenanthridin-6-one.

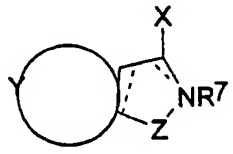
33. The compound of claim 1, wherein said compound is 5(*H*)2-nitro-10-bromophenanthridin-6-one.

34. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-10-nitrosophenanthridin-6-one.

35. The compound of claim 1, wherein said compound is 5(*H*)2-chloro-9,10-methylenedihydroxyphenan-thridin-6-one.

36. The compound of claim 1, wherein said compound is 5(*H*)2-nitro-9,10-methylenedihydroxyphenan-thridin-6-one.

37. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for

inhibiting PARP activity.

38. The composition of claim 37, wherein X is double-bonded oxygen.

39. The composition of claim 37, wherein Y represents the atoms necessary to form a fused benzene or naphthalene ring.

40. The composition of claim 37, wherein Y is substituted with at least one non-hydrogen, non-interfering substituent.

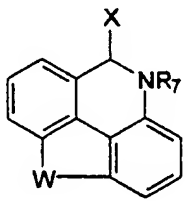
41. The composition of claim 37, wherein Z is: (i) $-CHR^2CHR^3-$, (ii) $-R^6C=CR^3-$, or (iii) $-R^2C=N-$.

42. The composition of claim 37, wherein Z is $-R^6C=CR^3-$ and forms a fused aromatic ring.

43. The composition of claim 37, wherein said ring is substituted with at least one non-hydrogen, non-interfering substituent.

44. The composition of claim 37, wherein R^7, when present, is hydrogen.

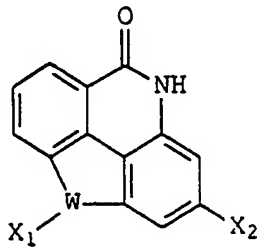
45. The composition of claim 37, wherein said compound has an isoquinoline, a pteridine, a phenanthridine, a phthalazine, or a quinazoline nucleus, or a tetracyclic bridging structure to ring Y, having the formula:



where W is -O-, -S-, $-NR^1-$, -CHO, -CHOH, or $CHNH_2$ where R^1 is hydrogen or lower alkyl.

46. The composition of claim 45, wherein said compound has a phenanthridine nucleus.

47. The composition of claim 37, wherein said compound has a tetracyclic bridging structure to ring Y, having the formula:



where W is -CH-; X_1 is hydrogen, hydroxy, or amino; and X_2 is hydrogen, amino, 1-piperidine, 1-piperazine, 1-imidazolidine, or hydroxy.

48. The composition of claim 37, wherein said compound has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 100 uM or lower.

49. The composition of claim 37, wherein said compound has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 25 uM or lower.

50. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a chloro group.

51. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a bromo group.

52. The composition of claim 37, wherein:

X is double bonded-oxygen;
Y is a fused benzene ring substituted with a nitro group; and
Z is $-R^6C=CR^3-$ where, R^6 and R^3, taken together, form a fused benzene ring substituted with an amino group.

53. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring with a bridging substituent connecting the Z ring with the Y ring.

54. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with an $-NO_2$ group.

55. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying at least one non-hydrogen, non-interfering substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form an unsubstituted fused benzene ring.

56. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying a chloro substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with a chloro group.

57. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^6, taken together, form a fused benzene ring substituted with a -Br and a $-NO_2$ group.

58. The composition of claim 37, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R_6C=CR^3-$ where R^6 and R^3, taken together, form a fused naphthalene ring.

59. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-10-methylphenanthridin-6-one.

60. The composition of claim 37, wherein said compound is 5(*H*)2-nitro-10-methylphenanthridin-6-one.

61. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-10-aminophenanthridin-6-one.

62. The composition of claim 37, wherein said compound is 5(*H*)2-nitro-10-aminophenanthridin-6-one.

63. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-10-nitrophenanthridin-6-one.

64. The composition of claim 37, wherein said compound is 5(*H*)2,10-dinitrophenanthridin-6-one.

65. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-10-hydroxyphenanthridin-6-one.

66. The composition of claim 37, wherein said compound is 5(*H*)2-nitro-10-hydroxyphenanthridin-6-one.

67. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-10-bromophenanthridin-6-one.

68. The composition of claim 37, wherein said compound is 5(*H*)2-nitro-10-bromophenanthridin-6-one.

69. The composition of claim 37, wherein said compound

is 5(*H*)2-chloro-10-nitrosophenanthridin-6-one.

70. The composition of claim 37, wherein said compound is 5(*H*)2-chloro-9,10-methlenedihydroxyphenan-thridin-6-one.

71. The composition of claim 37, wherein said compound is 5(*H*)2-nitro-9,10-methlenedihydroxy-2-phenan-thridin-6-one.

72. The composition of claim 37, wherein said composition is in the form of a capsule or tablet containing a single or divided dose of said agent, wherein said dose is sufficient to prevent or reduce the effects of vascular stroke or other neurodegenerative disease.

73. The composition of claim 37, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

74. The composition of claim 37, wherein said carrier comprises a biodegradable polymer.

75. The composition of claim 74, wherein said composition is a solid implant.

76. The composition of claim 74, wherein the biodegradable polymer releases the compound of formula I over a prolonged period of time.

77. The composition of claim 37, wherein said agent is present in an amount sufficient to treat or prevent neural tissue damage resulting from cerebral ischemia and reperfusion injury.

78. The pharmaceutical composition of claim 37 for treatment or prevention of diseases or conditions selected from the group consisting of tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage or diseases, neural tissue damage

resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders, muscular dystrophy, osteoarthritis, osteoporosis, chronic pain, acute pain, neuropathic pain, nervous insult, peripheral nerve injury, renal failure, retinal ischemia, septic shock, and skin aging, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence; or radiosensitizing tumor cells.

79. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:

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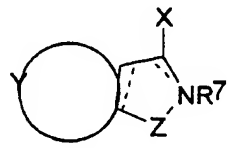


or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino,

dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;
(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;
(iii) $-R^2C=N-$;
(iv) $-CR^2(OH)-NR^7-$;
(v) $-C(O)-NR^7-$; or
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members; or

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for effecting neuronal activity.

80. The composition of claim 79, wherein the neuronal activity is not mediated by NMDA.

81. The composition of claim 79, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration, and treatment of a

neurological disorder.

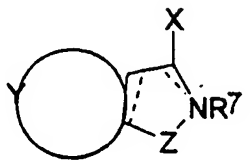
82. The composition of claim 81, wherein said neuronal activity is stimulation of damaged neurons resulting from cerebral ischemia or reperfusion injury.

83. The composition of claim 81, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, traumatic brain injury, physical damage to the spinal cord, stroke associated with brain damage, demyelinating disease and neurological disorder relating to neurodegeneration.

84. The composition of claim 83, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

85. The pharmaceutical composition of claim 83 for treatment or prevention of diseases or conditions selected from the group consisting of tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage or diseases, neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related macular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes, head trauma, immune senescence, inflammatory bowel disorders, muscular dystrophy, osteoarthritis, osteoporosis, chronic pain, acute pain, neuropathic pain, nervous insult, peripheral nerve injury, renal failure, retinal ischemia, septic shock, and skin aging, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

86. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:



I

or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the

ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_8 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating inflammatory bowel disorders.

87. The composition of claim 86, wherein said inflammatory bowel disorder is colitis.

88. The composition of claim 86, wherein said inflammatory bowel disorder is Crohn's disease.

89. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:

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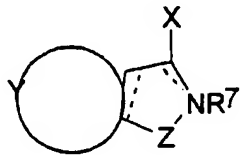

or a pharmaceutically acceptable base or acid addition salt,

hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle,

heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating cardiovascular disorders.

90. The composition of claim 89, wherein said cardiovascular disorder is selected from the group consisting of coronary artery disease, angina pectoris, myocardial infarction, cardiogenic shock, and cardiovascular tissue damage.

91. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:

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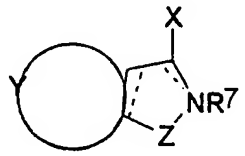

or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine,

imidazolidine, alkyl, aryl, or aralkyl;
(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;
(iii) $-R^2C=N-$;
(iv) $-CR^2(OH)-NR^7-$; or
(v) $-C(O)-NR^7-$;
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;
and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating septic shock.

92. The composition of claim 91, wherein said septic shock is endotoxic shock.

93. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:

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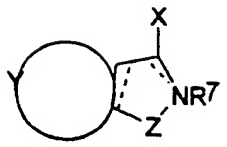


or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

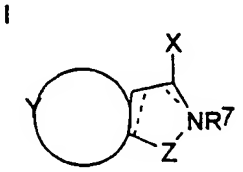
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo,

hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating diabetes.

94. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position

and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

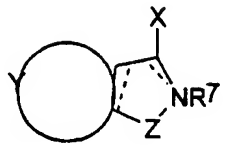
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating arthritis.

95. A pharmaceutical composition comprising a compound

of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo,

hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

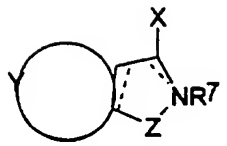
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for treating cancer.

96. The composition of claim 95, wherein said cancer is selected from the group consisting of: ACTH-producing tumors, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head & neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovary cancer, ovary (germ cell) cancer, prostate cancer, pancreatic cancer, penis cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva and Wilm's tumor.

97. A pharmaceutical composition comprising a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, -

NO_2, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

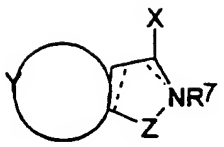
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino;

and a pharmaceutically acceptable carrier, wherein the compound of formula I is present in an amount effective for radiosensitizing tumor cells.

98. The composition of claim 97, wherein said tumor cells are selected from the group consisting of: ACTH-producing tumors, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head & neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovary cancer, ovary (germ cell) cancer, prostate cancer, pancreatic cancer, penis cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva and Wilm's tumor.

99. A method of inhibiting PARP activity comprising administering a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo,

hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

100. The method of claim 99, wherein X is double-bonded oxygen.

101. The method of claim 99, wherein Y has at least one site of unsaturation.

102. The method of claim 99, wherein Y represents the atoms necessary to form a fused benzene or naphthalene ring.

103. The method of claim 99, wherein Y is substituted with at least one non-hydrogen, non-interfering substituent.

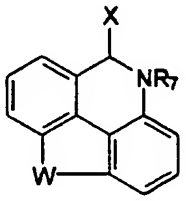
104. The method of claim 99, wherein Z is: (i) $-CHR^2CHR^3-$, (ii) $-R^6C=CR^3-$, or (iii) $-R^2C=N-$.

105. The method of claim 99, wherein Z is $-R^6C=CR^3-$ and forms a fused aromatic ring.

106. The method of claim 99, wherein said ring is substituted with at least one non-hydrogen, non-interfering substituent.

107. The method of claim 99, wherein, when R^7 is present, it is hydrogen.

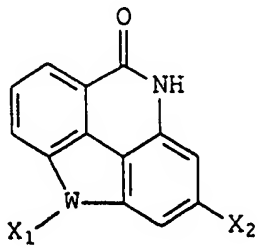
108. The method of claim 99, wherein said compound has an isoquinoline, a pteridine, a phenanthridine, a phthalazine, or a quinazoline nucleus, or a tetracyclic bridging structure to ring Y, having the formula:



where W is -O-, -S-, $-NR^1-$, -CHO, -CHOH, or $CHNH_2$ where R^1 is hydrogen or lower alkyl.

109. The method of claim 99, wherein said compound has a phenanthridine nucleus.

110. The composition of claim 99, wherein said compound has a tetracyclic bridging structure to ring Y, having the formula:



where W is -CH-; X_1 is hydrogen, hydroxy, or amino; and X_2 is hydrogen, amino, 1-piperidine, 1-piperazine, 1-imidazolidine, or hydroxy.

111. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a

fused benzene ring substituted with a chloro group.

112. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a bromo group.

113. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring substituted with a nitro group; and
Z is $-R^6C=CR^3-$ where, R^6 and R^3, taken together, form a fused benzene ring substituted with an amino group.

114. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring with a bridging substituent connecting the Z ring with the Y ring.

115. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with an $-NO_2$ group.

116. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying at least one non-hydrogen, non-interfering substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form an unsubstituted fused benzene ring.

117. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying a chloro substituent; and

Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with a chloro group.

118. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^6, taken together, form a fused benzene ring substituted with a -Br and a $-NO_2$ group.

119. The method of claim 99, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R_6C=CR^3-$ where R^6 and R^3, taken together, form a fused naphthalene ring.

120. The method of claim 99, wherein said compound has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 100 uM or lower.

121. The method of claim 99, wherein said compound has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 25 uM or lower.

122. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-methylphenanthridin-6-one.

123. The method of claim 99, wherein said compound is 5(*H*)2-nitro-10-methylphenanthridin-6-one.

124. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-aminophenanthridin-6-one.

125. The method of claim 99, wherein said compound is 5(*H*)2-nitro-10-aminophenanthridin-6-one.

126. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-nitrophenanthridin-6-one.

127. The method of claim 99, wherein said compound is 5(*H*)2,10-dinitrophenanthridin-6-one.

128. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-hydroxyphenanthridin-6-one.

129. The method of claim 99, wherein said compound is 5(*H*)2-nitro-10-hydroxyphenanthridin-6-one.

130. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-bromophenanthridin-6-one.

131. The method of claim 99, wherein said compound is 5(*H*)2-nitro-10-bromophenanthridin-6-one.

132. The method of claim 99, wherein said compound is 5(*H*)2-chloro-10-nitrosophenanthridin-6-one.

133. The method of claim 99, wherein said compound is 5(*H*)2-chloro-9,10-methlenedihydroxyphenanthridin-6-one.

134. The method of claim 99, wherein said compound is 5(*H*)2-nitro-9,10-methlenedihydroxyphenanthridin-6-one.

135. The method of claim 99, wherein said composition is in the form of a capsule or tablet containing a single or divided dose of said compound, wherein said dose is sufficient to prevent or reduce the effects of vascular stroke or other neurodegenerative disease.

136. The method of claim 99, wherein said composition is administered as a sterile solution, suspension or emulsion, in a single or divided dose.

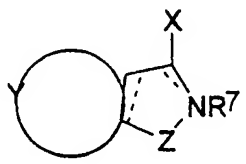
137. The method of claim 99, wherein said composition is administered as a solid implant capable of releasing the

compound over a prolonged period of time.

138. The method of claim 99, wherein said compound is present in an amount sufficient to treat or prevent neural tissue damage resulting from cerebral ischemia and reperfusion injury.

139. A method of effecting a neuronal activity in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine,

piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

140. The method of claim 139, wherein the neuronal activity is not mediated by NMDA.

141. The method of claim 139, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration, and treatment of a neurological disorder.

142. The method of claim 141, wherein said neuronal activity is stimulation of damaged neurons resulting from cerebral ischemia or reperfusion injury.

143. The method of claim 141, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, traumatic brain injury, physical damage to the spinal cord, stroke associated with brain damage, demyelinating disease and neurological disorder relating to neurodegeneration.

144. The method of claim 143, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

145. A method of treating an inflammatory bowel disorder in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring nitrogen:

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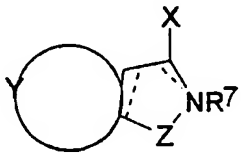

or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine,

imidazolidine, alkyl, aryl, or aralkyl;
(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;
(iii) $-R^2C=N-$;
(iv) $-CR^2(OH)-NR^7-$; or
(v) $-C(O)-NR^7-$;
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

146. The method of claim 145, wherein said bowel disorder is colitis.

147. The method of claim 145, wherein said inflammatory bowel disorder is Crohn's disease.

148. A method of treating a cardiovascular disorder in an animal comprising administering to said animal an

effective amount of a compound of formula I containing at least one ring nitrogen:

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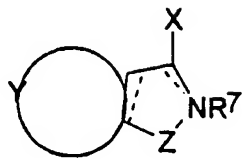


or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the

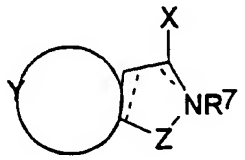
ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

149. The method of claim 148, wherein said cardiovascular disorder is selected from the group consisting of coronary artery disease, angina pectoris, myocardial infarction, cardiogenic shock, and cardiovascular tissue damage.

150. A method of treating septic shock in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

(v) $-C(O)-NR^7-$;

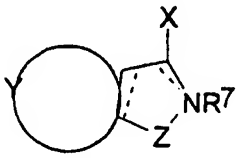
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

151. The method of claim 150, wherein said septic shock is endotoxic shock.

152. A method of treating diabetes in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring

members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$; or

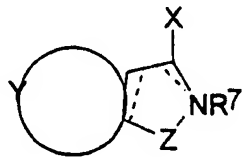
(v) $-C(O)-NR^7-$;

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

153. A method of treating arthritis in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-,

bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

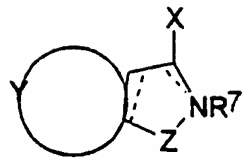
(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

154. A method of treating cancer in an animal comprising administering to said animal an effective amount of a compound of formula I containing at least one ring

nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently

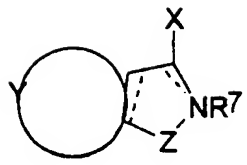
hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, -NO_2, -$COOR^7$, or -NR^7R^8 where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino.

155. The method of claim 154, wherein said cancer is selected from the group consisting of: ACTH-producing tumors, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head & neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovary cancer, ovary (germ cell) cancer, prostate cancer, pancreatic cancer, penis cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva and Wilm's tumor.

156. A process for preparing a compound of formula I containing at least one ring nitrogen:

I



or a pharmaceutically acceptable base or acid addition salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixtures thereof, wherein:

X is double-bonded oxygen or -OH;

when R^7 is present, it is hydrogen or lower alkyl;

Y represents the atoms necessary to form a fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; and

Z is (i) $-CHR^2CHR^3-$ wherein R^2 is in the meta-position and R^3 is in the ortho-position relative to said ring nitrogen of formula I, and R^2 and R^3 are independently hydrogen, hydroxy, amino, dimethylamino, nitro, piperidine, piperazine, imidazolidine, alkyl, aryl, or aralkyl;

(ii) $-R^6C=CR^3-$ wherein R^6 is meta to the ring nitrogen, and R^3 and R^6 are independently hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, amino, dimethylamino, piperidine, piperazine, imidazolidine, $-NO_2$, $-COOR^7$, or $-NR^7R^8$ where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^6 and R^3, taken together, form a fused aromatic ring, wherein each individual ring has 5-6 ring members;

(iii) $-R^2C=N-$;

(iv) $-CR^2(OH)-NR^7-$;

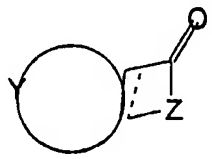
(v) $-C(O)-NR^7-$; or

(vi) $-NR^9-C(O)-CHR^{10}-$ wherein R^{10} is ortho to the ring nitrogen, and R^9 and R^{10} are independently

hydrogen, lower alkyl, aryl, aralkyl, halo, hydroxy, piperidine, piperazine, imidazolidine, -NO_2, -$COOR^7$, or -NR^7R^8 where R^8 is independently hydrogen or C_1-C_9 alkyl, or R^9 and R^{10}, taken together, form a fused ring, wherein each individual ring has 5-7 ring members;

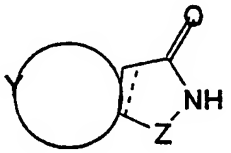
wherein said alkyl, aryl, and aralkyl, are substituted at one or more positions with hydrogen, hydroxy, halo, haloalkyl, alkoxy, alkenoxy, alkaryloxy, aryloxy, arylalkoxy, cyano, amino, imino, sulfhydryl, thioalkyl, carboxy, carbocycle, heterocycle, lower alkyl, lower alkenyl, cycloalkyl, aryl, arylalkyl, haloaryl, amino, nitro, nitroso, dimethylamino; and said process comprising the step of reacting a compound of formula IV:

IV



with a nitrogen-insertion agent to form a compound of formula V:

V



157. The process of claim 156, wherein said compound

has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 100 μM or lower.

158. The process of claim 156, wherein said compound has an IC_{50} for inhibiting poly(ADP-ribose) polymerase *in vitro* of 25 μM or lower.

159. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a chloro group.

160. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring substituted with a bromo group.

161. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring substituted with a nitro group; and
Z is $-R^6C=CR^3-$ where, R^6 and R^3, taken together, form a fused benzene ring substituted with an amino group.

162. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^3 and R^6, taken together, form a fused benzene ring with a bridging substituent connecting the Z ring with the Y ring.

163. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with an $-NO_2$ group.

164. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying at least one non-hydrogen, non-interfering substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form an unsubstituted fused benzene ring.

165. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring carrying a chloro substituent; and
Z is $-R^6C=CR^3-$ where R^6 and R^3, taken together, form a fused benzene ring substituted with a chloro group.

166. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R^6C=CR^3-$ where R^6 and R^6, taken together, form a fused benzene ring substituted with a -Br and a -NO_2 group.

167. The process of claim 156, wherein:
X is double bonded-oxygen;
Y is a fused benzene ring; and
Z is $-R_6C=CR^3-$ where R^6 and R^3, taken together, form a fused naphthalene ring.

168. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-methylphenanthridin-6-one.

169. The process of claim 156, wherein said compound is 5(*H*)2-nitro-10-methyl-2-phenanthridin-6-one.

170. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-amino-phenanthridin-6-one.

171. The process of claim 156, wherein said compound is 5(*H*)2-nitro-10-amino-phenanthridin-6-one.

172. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-nitrophenanthridin-6-one.

173. The process of claim 156, wherein said compound is 5(*H*)2,10-dinitrophenanthridin-6-one.

174. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-hydroxyphenanthridin-6-one.

175. The process of claim 156, wherein said compound is 5(*H*)2-nitro-10-hydroxyphenanthridin-6-one.

176. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-bromophenanthridin-6-one.

177. The process of claim 156, wherein said compound is 5(*H*)2-nitro-10-bromophenanthridin-6-one.

178. The process of claim 156, wherein said compound is 5(*H*)2-chloro-10-nitrosophenanthridin-6-one.

179. The process of claim 156, wherein said compound is 5(*H*)2-chloro-9,10-methlenedihydroxyphenan-thridin-6-one.

180. The process of claim 156, wherein said compound is 5(*H*)2-nitro-9,10-methlenedihydroxyphenan-thridin-6-one.

181. The process of claim 156, wherein said nitrogen insertion agent comprises a mixture of NaN_3 and a strong acid.

182. The process of claim 181, wherein said acid is H_2SO_4.

183. The compounds, compositions, methods, and processes as described herein.

FIG. 1

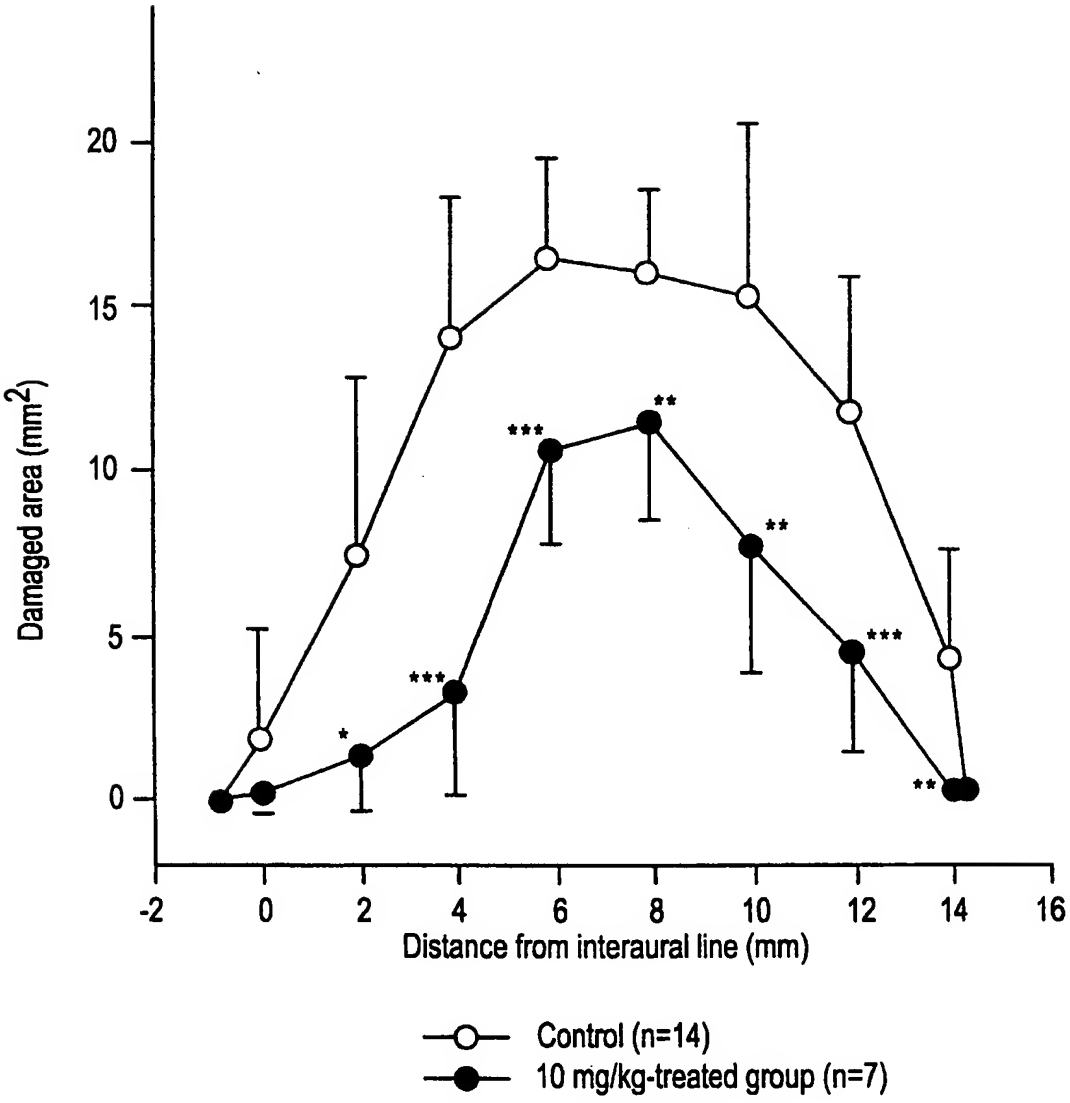
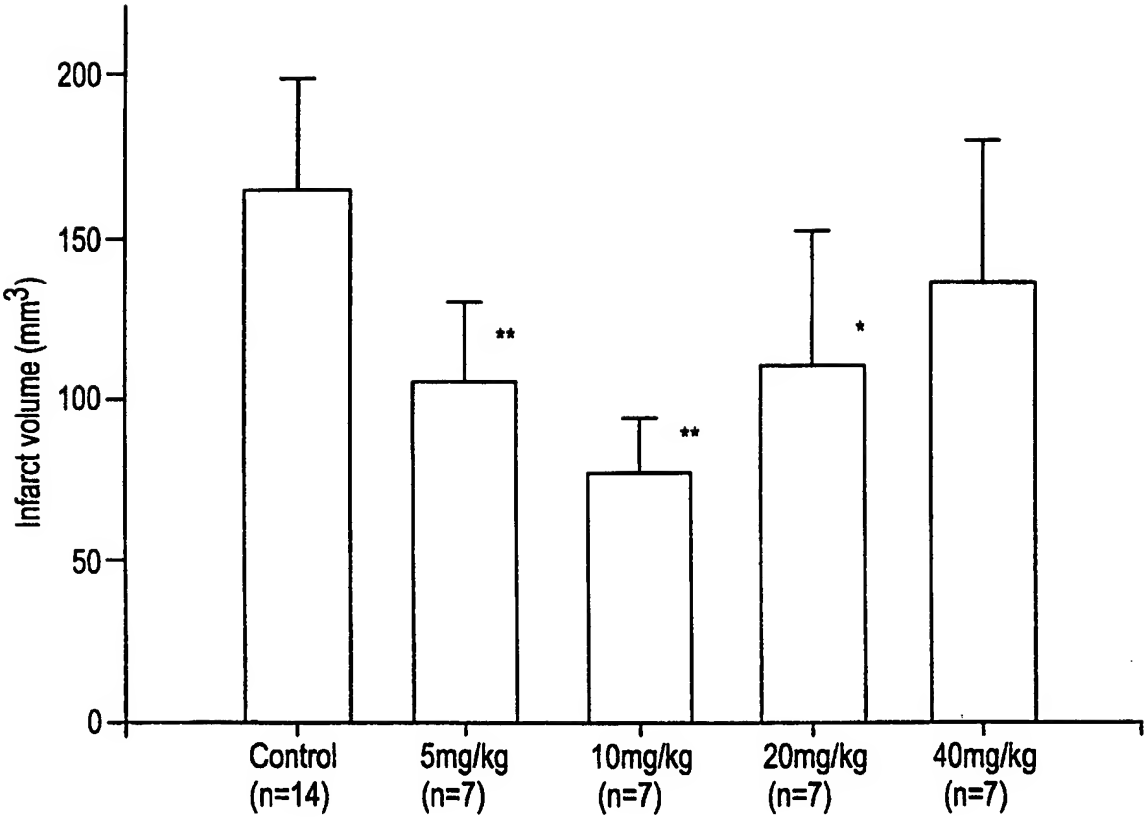

Damaged area (mm2)
20
15
10
5
0
-2
0
2
4
6
8
10
12
14
16
Distance from interaural line (mm)
*
***
***
**
**
***
**
Control (n=14)
10 mg/kg-treated group (n=7)

FIG. 2


Infarct volume (mm3)
200
150
100
50
0
**
**
*
Control (n=14)
5mg/kg (n=7)
10mg/kg (n=7)
20mg/kg (n=7)
40mg/kg (n=7)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/18195

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/12 C07D221/16 C07D221/18 A61K31/47 C07D491/04 C07D217/24 C07D237/32 C07D475/02 //(C07D491/04,317:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 85, no. 21, 22 November 1976 Columbus, Ohio, US; abstract no. 159898a, column 531; XP002087394 see abstract & SU 514 825 A (A.V.UPADYSSHEVA ET AL) 25 May 1976 ---	1,2
X	US 3 291 801 A (STEWART R. MONTGOMERY) 13 December 1966 see the whole document ---	1-4,7-11
X	US 3 932 643 A (GAUTHIER GEORGE J) 13 January 1976 see the whole document ---	1-11, 37-46
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 1998	29/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/US 98/18195

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 1 880 441 A (RUDOLF M. HEIDENREICH ET AL) 4 October 1932 see the whole document	1-4,7-11
X	ROBERT GRANGER ET AL: "Transposition de Beckmann de la cis-bicyclo'3.3.0!octanoxime-2" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE.,1962, pages 233-234, XP002087389 PARIS FR see compound II,page 233	1,2
X	K.APARJITAN ET AL: "Thiaindanones III. Beckmann rearrangement of oximes" JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 3, December 1966, pages 466-469, XP002087390 PROVO US see age 466,compound II,pge 469	1,2
X	DONALD J. DUMADS: "Total synthesis of peramine" JOURNAL OF ORGANIC CHEMISTRY., vol. 5, no. 20, 1988, pages 4650-4653, XP002087391 EASTON US see page 4650,compound 6,page4652	1,2
X	MICHAEL M. ROBISON ET AL: "Reaction of 1-chloroisoquinoline with peracetic acid" JOURNAL OF ORGANIC CHEMISTRY., vol. 23, July 1958, pages 1071-1072, XP002087392 EASTON US see the whole document	1-10
X	FR 2 205 333 A (LABORATORIO GUIDOTTI & C SPA) 31 May 1974 see claims	1-11, 37-46
X	CHEMICAL ABSTRACTS, vol. 62, no. 5, 1 March 1965 Columbus, Ohio, US; abstract no. 5271c, ZOFIA TAALIK ET AL: "Some pyridotriazoles and imidazoles" XP002087395 see abstract & ROCZNIKI CHEM., vol. 38, no. 5, pages 887-888,	1,2

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INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/US 98/18195

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HSI-LUNG PAN ET AL: "6(5H)-phenanthridinones.III.Halo-6(5H)phenanthridinones(1,2)" JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 7, June 1970, pages 597-605, XP002087393 PROVO US see the whole document ---	1-11
X	CHEMICAL ABSTRACTS, vol. 88, no. 13, 27 March 1978 Columbus, Ohio, US; abstract no. 89502c, N.S.DOKUNIKHIN ET AL: "Derivatives of cyclopenta'k,l,m!phenanthridine" page 505; XP002087396 see abstract & ZH.VSES.KHIM.O-VA, vol. 22, no. 6, pages 706-707, ---	1-3,10, 12
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A	WO 95 24379 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 14 September 1995 see claims ---	1,37-155
A	US 5 589 483 A (WEST MICHAEL D) 31 December 1996 see the whole document ---	1,37-155
A	BANASIK M ET AL: "Specific inhibitors of poly(ADP-ribose)synthetase and mono(ADP-ribosyl)transferase" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 3, 25 January 1992, pages 1569-1575, XP000574735 cited in the application see the whole document --- -/--	1,37-155

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/US 98/18195

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GRIFFIN R J ET AL: "Novel potent inhibitors of the DNA repair enzyme poly(ADP-ribose)polymerase (PARP)" ANTI-CANCER DRUG DESIGN, vol. 10, no. 6, September 1995, pages 507-514, XP002065156 see the whole document ---	1,37-155
A	M.J.SUTO ET AL: "Dihydroisoquinolinones:the design and synthesis of a new seies of potent inhibitors of poly(ADP-ribose)polymerase" ANTI-CANCER DRUG DESIGN, vol. 7, 1991, pages 107-117, XP002086825 cited in the application see the whole document -----	1,37-155

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 18195

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 99-155
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 99-155 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

THE search revealed such a large number of particularly relevant documents,in particular with regard to novelty,that the drafting of acomprehensive International Search Report is not feasible.The cited documents are considered as to form a representative sample of the revealed documents,duly taking into account their relevance with respect to the subject matter as illustrated by the examples

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No
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